Synthesis of Heteroaryl Sulfonamides from Organozinc Reagents and 2,4,6-Trichlorophenyl Chlorosulfate

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Supporting Information

General Information

All reactions were carried out under an argon atmosphere in flame-dried or oven-dried glassware unless otherwise specified. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. Commercial materials were used without additional purification unless otherwise specified. The part number for the oven-dried culture tubes used was Fisher 20 x 150 mm tubes (Cat. No. 1495937C); for plastic screw top caps, CLOSURE OT S/T 18-400TH 14 (Cat. No. 033407G); and for septa that fit into the screw cap tops, Thermo Scientific SPTA SPTA PTFE/SIL F/18-400 10 (Cat. No. 03394B).

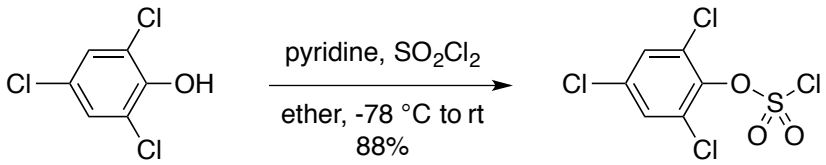
Reagents: Tetrahydrofuran (THF) was purchased from J. T. Baker in CYCLE-TAINER™ containers and then vigorously purged with argon for one hour and passed through two activated alumina columns. Triethylamine was purchased from J. T. Baker. Zinc chloride solution (1.9M in 2-methyl tetrahydrofuran), *n*-butyl lithium solution (2.5M in hexanes), isopropylmagnesium chloride lithium chloride complex solution (1.3 M in THF) (Turbo Grignard), 2-pyridylzinc bromide solution (0.5M in THF), 2-thienylzinc bromide solution (0.5M in THF), lithium bis(trimethylsilyl)amide (LHMDS) solution (1.0 M in THF), aniline, sulfuryl chloride, 2,6-dibromopyridine, morpholine, benzylamine, *N*-methylaniline, 2-aminothiazole, 2,4,6-trichlorophenol, thianaphthene, 2,4,6-trimethylbromobenzene, 2,3-benzofuran, *tert*-butyl 1*H*-indole-1-carboxylate, hexanes, ethyl acetate (EtOAc), dichloromethane, and methanol (MeOH) were purchased from Sigma Aldrich. 2,5-Dibromothiophene, 2-bromo-6-(trifluoromethyl)pyridine, and 4-bromopyrazole were purchased from Oakwood Chemical. 2-Bromopyridine was purchased from Oakwood Chemical and distilled over calcium hydride under reduced pressure and stored under an argon atmosphere prior to use. 2-Bromo-3-methylpyridine was purchased from Acros. Cyclohexylamine and 1-bromo-2-isopropylbenzene were purchased from Alfa Aesar. 2-Aminomethylpyridine was purchased from Avocado. Ammonium hydroxide solution was purchased from Macron Fine Chemicals. $CDCl_3$, CD_3OD, and $(CD_3)_2SO$ were purchased from Cambridge Isotope Laboratories. 2-Iodopyrimidine,[1] 4-bromo-1-trityl-1*H*-pyrazole, [2] 1-(triisopropylsilyl)-1H-pyrrole, [3] and 3-bromo-1-(triisopropylsilyl)-1*H*-pyrrole[4] were prepared according to literature procedures.

Analytical Data: Compounds were characterized by melting point, ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, elemental analysis, mass spectrometry, and/or high-resolution mass spectrometry. Nuclear Magnetic Resonance spectra were obtained on Varian 500 MHz instruments at ambient temperature. Chemical shifts for ^{1}H- and ^{13}C-NMR were reported in parts per million (ppm) relative to solvent signals ($CDCl_3$: 7.26 for ^{1}H-NMR and 77.16 for ^{13}C-NMR; CD_3OD: 3.31 for ^{1}H-NMR and 49.00 for ^{13}C-NMR; $(CD_3)_2SO$: 2.50 for ^{1}H-NMR and 39.52 for ^{13}C-NMR). Multiplicities were abbreviated in the following ways: “s” for singlet; “bs” for broad singlet; “d” for doublet; “t” for triplet; “q” for quartet; “h” for heptet; and “m” for multiplet. All

[1] Vlád, G.; Horváth, I. T. *J. Org. Chem.* **2002**, *67*, 6550-6552.
[2] Cheung, C. W.; Surry, D. S.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3734-3737.
[3] Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446-4456.
[4] Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653-1656.

IR spectra were taken on a Thermo Scientific – Nicolet iS5 spectrometer (iD5 ATR – diamond). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. High resolution mass spectrometry data was collected on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points were measured on a Stanford Research Sytems EZ-Melt MPA120 automated melting point system. Column chromatography was performed using a Biotage SP4 apparatus with pre-packed silica cartridges. Chemical yields refer to isolated yields of compounds analyzed by elemental analysis or high-resolution mass spectrometry.

Preparation of 2,4,6-Trichlorophenylchlorosulfate (TCPC)



50 mmol **TCPC**

The following procedure was directly adapted from the previously reported synthesis of phenylchlorosulfate.[5]

2,4,6-trichlorophenol (10g, 50 mmol, 1 equiv.) was added to an oven-dried 500 mL round bottom flask with large magnetic stir bar. The flask was fitted with a rubber septum and then was evacuated and back-filled with argon (the purging procedure was repeated a total of three times). The flask was charged with ether (200 mL) and pyridine (4.1 mL, 50 mmol, 1 equiv.). The flask was put into a -78 °C (dry ice/acetone) bath with magnetic stirring. Upon cooling, solids formed in the mixture. The mixture was then charged with sulfuryl chloride (4.2 mL, 50 mmol, 1 equiv.) in small portions over 10 min. The mixture was allowed to warm overnight with magnetic stirring. The mixture was then filtered through a plug of celite with ether (300 mL), concentrated, adsorbed onto silica gel, and purified by silica gel chromatography with a Biotage instrument (100g SNAP column, 0 – 5% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford 2,4,6-trichlorophenyl chlorosulfate (TCPC) as a colorless oil (13.057g, 88%). The compound is thermally sensitive, and should be stored in a freezer. Extended heating during isolation, such as with a ≥25 °C water bath used with a rotary evaporator when concentrating either the crude, filtered reaction mixture or after chromatography, will result in slight decomposition and the formation of a yellow or orange oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 2H).
^{13}C NMR (126 MHz, $CDCl_3$): δ 142.8, 134.9, 130.6, 129.7.
Elemental Analysis: Anal. calcd. for $C_6H_2Cl_4O_3S$: C, 24.35; H, 0.68. Found: C, 24.60; H, 0.65.
IR (neat, cm^{-1}): 1738, 1564, 1421, 1218, 1191, 1131, 883, 858, 802, 739, 667, 604.

[5] DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *15*, 10638-10641.

General Procedures (Schemes 2-4)

General Procedure A: Preparation of 2,4,6-trichlorophenyl pyridine-2-sulfonates (Scheme 2)

An oven-dried culture tube (Fisher 20 x 150 mm tubes; Cat. No. 1495937C) with a Teflon septum (Thermo Scientific SPTA SPTA PTFE/SIL F/18-400 10; Cat. No. 03394B) and screw cap (CLOSURE OT S/T 18-400TH 14; Cat. No. 033407G) and magnetic stir bar was charged with solid 2-bromopyridine analog. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid compounds were added after purging with argon). THF was added (2 mL/mmol bromopyridine), and the tube was put in an acetone/dry ice bath with magnetic stirring and argon inlet. *n*-Butyllithium solution (2.5M in hexanes, 1 equiv.) was added dropwise via syringe over 5 min and the mixture was stirred in the cold bath for an additional 15 min. Zinc chloride solution (1.9M in 2-methyltetrahydrofuran, 1 equiv.) was added dropwise via syringe over 5 min. (Care must be taken to add *n*-butyllithium and zinc chloride solutions slowly, as the exotherm that results from too rapid of an addition of either reagent decomposes the sensitive 2-pyridyllithium species.) The tube was then removed from the cold bath and the mixture stirred at room temperature for the remainder of 1 h. The tube was placed in an ice/water bath and TCPC (1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The tube was removed from the ice/water bath and the mixture was diluted with ethyl acetate (10 mL), water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

General Procedure B: Preparation of 2-pyridyl sulfonamides from 2,4,6-trichlorophenyl pyridine-2-sulfonate (4a) and alkylamines (Scheme 3)

An oven-dried culture tube with a Teflon septum and screw cap (all the same part numbers as in General Procedure A) and magnetic stir bar was charged with 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a**. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times). THF was added (3 ml/mmol ester), then amine for liquid amines or aqueous ammonium hydroxide. The punctured septum was replaced with a new septum, and the tube was put in a 60 °C oil bath with magnetic stirring for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

General Procedure C: Preparation of 2-pyridyl sulfonamides from 2,4,6-trichlorophenyl pyridine-2-sulfonate (4a) and arylamines (Scheme 3)

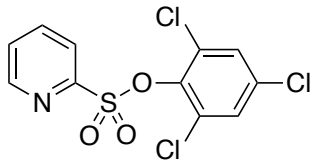
An oven-dried culture tube with a Teflon septum and screw cap (all the same part numbers as in General Procedure A) and magnetic stir bar was charged with 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (1 equiv.) and solid arylamine (1.2 or 2 equiv.). The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid arylamines were added after purging with argon). THF was added (2 ml/mmol ester), and then the tube was put in an ice/water bath with magnetic stirring. LHMDS solution (1.2 or 2 equiv., same as arylamine) was added dropwise over 5 min. After the remainder of an hour, with the ice/water bath being allowed to warm naturally, the mixture was diluted with MeOH (10 mL). The mixture was concentrated under reduced pressure, adsorbed onto the silica gel, and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

General Procedure D: Preparation of aryl and heteroaryl sulfonamides (Scheme 4)

An oven-dried culture tube with a Teflon septum and screw cap and magnetic stir bar (all the same part numbers as in General Procedure A) was charged with solid aryl or heteroaryl bromide or heteroarene. The tube was then evacuated and back-filled with argon (this process was repeated a total of three times; liquid compounds were added after purging with argon). THF was added (2 ml/mmol bromide or heteroarene), and the tube was put in an acetone/dry ice bath with magnetic stirring and argon inlet. *n*-Butyllithium solution (400 µL, 2.5M in hexanes, 1 mmol, 1 equiv.) was added dropwise via needle/syringe over 5 min and the mixture was stirred in the cold bath for the remainder of 1 h. Zinc chloride solution (530 µL, 1.9M in 2-methyltetrahydrofuran, 1 mmol, 1 equiv.) was added dropwise via needle/syringe over 5 min. (Care must be taken to add *n*-butyllithium and zinc chloride solutions slowly, as the exotherm that results from too rapid of an addition of either reagent may decompose the aryllithium species.) The tube was then removed from the cold bath and the mixture stirred at room temperature for the remainder of 1 h. The tube was placed in an ice/water bath and TCPC (175 µL, 1 mmol, 1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The ice/water bath was refreshed and then the appropriate amine (2 mmol, 2 equiv.) was added dropwise via needle/syringe to the reaction mixture. After one hour the ice/water bath was removed and the mixture was stirred until the reaction was complete as determined by analytical thin-layer chromatography (TLC), typically an additional 1 h. The mixture was diluted with ethyl acetate (10 mL) water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The material was then adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (50 g SNAP column).

Preparation and Characterization of Compounds in Scheme 2

2,4,6-Trichlorophenyl pyridine-2-sulfonate (4a)



4a

According to General Procedure A, 2-bromopyridine (1.9 mL, 20 mmol) was reacted sequentially with *n*-butyllithium solution (8 mL, 2.5 M in hexanes, 20 mmol), $ZnCl_2$ solution (10.6 mL, 1.9 M in 2-MeTHF, 20 mmol), and TCPC (3.5 mL, 20 mmol). Diverging from the general procedure, a flame-dried 200 mL round-bottom flask with rubber septum was substituted for the culture tube. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 100 g SNAP column, 0 – 60% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4a** as an off-white solid (first run: 5.04 g, 74%; second run: 5.02 g, 74%). See Figure S1 (below) for a picture of the material on a piece of weighing paper.

M.p. (°C): 92 – 99.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.80 (ddt, J = 4.7, 1.7, 0.8 Hz, 1H), 8.09 (dq, J = 7.9, 0.9 Hz, 1H), 8.01 (tdd, J = 7.8, 1.8, 0.7 Hz, 1H), 7.65 (ddt, J = 7.6, 4.7, 0.9 Hz, 1H), 7.33 (d, J = 0.7 Hz, 2H).
^{13}C NMR (126 MHz, Chloroform-d): δ 154.6, 150.6, 142.4, 138.5, 133.2, 130.75, 129.3, 128.6, 123.9.
Elemental Analysis: Anal. calcd. for $C_{11}H_6Cl_3NO_3S$: C, 39.02; H, 1.79. Found: C, 38.96; H, 1.93.
IR (neat, cm^{-1}): 1738, 1561, 1442, 1380, 1259.50, 1227, 1189, 1113, 1089, 993, 858, 778, 739, 649.

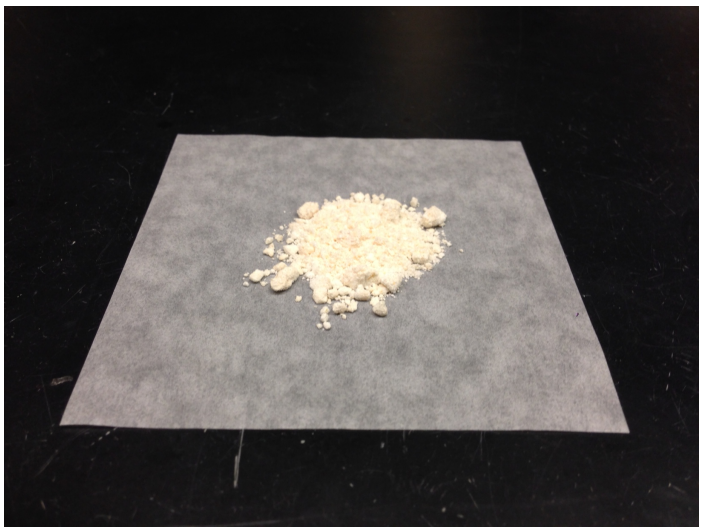
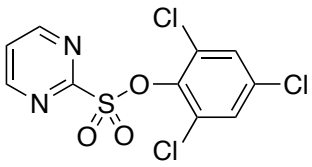


Figure S1. 2,4,6-Trichlorophenyl pyridine-2-sulfonate **4a**

2,4,6-Trichlorophenyl pyrimidine-2-sulfonate (4b)



4b

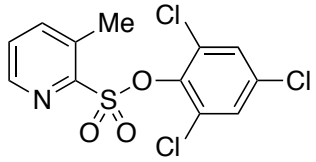
The following Grignard synthesis protocol was adapted from a literature procedure.[6] An oven-dried culture tube with magnetic stir bar and screw cap with teflon septum (same part numbers as in General Procedure A) was charged 2-iodopyrimidine (206 mg, 1.0 mmol). The tube was evacuated and back-filled with argon (this procedure was repeated a total of three times). THF (3 mL) was added, and the tube was put in an ice water bath with magnetic stirring. Isopropylmagnesium chloride lithium chloride complex (Turbo Grignard) solution (770 µL, 1.3 M in THF, 1.0 mmol) was added dropwise via needle/syringe over 5 min. The mixture was stirred for 1 h with the tube in the

[6] Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 5528-5531.

ice/water bath. $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol) was then added dropwise over 5 min via needle/syringe, and the mixture was stirred at rt for 15 min. The tube was placed in an ice/water bath and TCPC (1 equiv.) was added dropwise via syringe over 5 min. The mixture was stirred in the ice/water bath for 2 h, and the bath was allowed to slowly warm over this time period. The tube was removed from the ice/water bath and the mixture was diluted with ethyl acetate (10 mL), water (5 mL), and brine (5 mL). The layers were separated and the aqueous layer was washed another two times with ethyl acetate (2*10 mL). The collected organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was adsorbed onto silica gel and purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 60% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4b** as a white solid (first run: 97.4 mg, 29%; second run: 107 mg, 32%).

M.p. (°C): 120 – 123.
^{1}H-NMR (500 MHz, DMSO-d6): δ 9.19 (d, J = 5.0 Hz, 1H), 8.06 – 7.98 (m, 2H), 7.88 (s, 2H).
^{13}C NMR (126 MHz, DMSO-d6): δ 161.8, 159.9, 141.8, 132.9, 129.6, 129.5, 126.1.
Elemental Analysis: Anal. calcd. for $C_{10}H_5Cl_3N_2O_3S$: C, 35.37; H, 1.48. Found: C, 35.46; H, 1.65.
IR (neat, cm^{-1}): 3072, 1738, 1585, 1442, 1380, 1233, 1212, 1152, 1134, 989, 897, 874, 859, 824, 794, 739, 660, 604.

2,4,6-Trichlorophenyl 3-methylpyridine-2-sulfonate (4c)

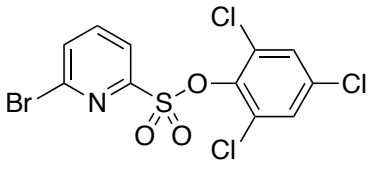


4c

According to General Procedure A, 2-bromo-3-methylpyridine (120 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), and TCPC (175 µL, 1 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 100 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4c** as white solid (first run: 241 mg, 68%; second run: 196.5 mg, 56%).

M.p. (°C): 118 – 120.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.55 (ddd, J = 4.6, 1.5, 0.7 Hz, 1H), 7.80 (ddt, J = 7.8, 1.6, 0.7 Hz, 1H), 7.52 (dd, J = 7.7, 4.5 Hz, 1H), 7.32 (s, 2H), 2.80 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-d): δ 153.4, 146.9, 142.6, 141.6, 135.1, 133.1, 130.8, 129.2, 128.4, 19.6.
Elemental Analysis: Anal. calcd. for $C_{12}H_8Cl_3NO_3S$: C, 40.88; H, 2.29. Found: C, 40.77; H, 2.44.
IR (neat, cm^{-1}): 1738, 1566, 1443, 1420, 1385, 1225, 1200, 1167, 1134, 986, 875, 858, 801, 771, 738, 724, 663, 650, 608, 585.

2,4,6-Trichlorophenyl 6-bromopyridine-2-sulfonate (4d)



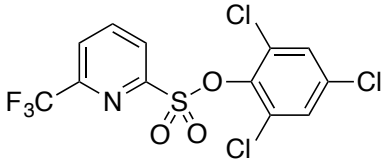
4d

According to General Procedure A, 2,6-dibromopyridine (240 mg, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol),

and TCPC (175 µL, 1 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4d** as a white solid (first run: 236.8 mg, 57%; second run: 204 mg, 49%).

M.p. (°C): 149 – 152.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.06 (dt, J = 7.4, 1.1 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.38 – 7.35 (m, 2H).
^{13}C NMR (126 MHz, Chloroform-d): δ 154.6, 142.8, 142.4, 140.2, 133.5, 133.4, 130.7, 129.4, 122.7.
Elemental Analysis: Anal. calcd. for $C_{11}H_5Cl_3NO_3S$: C, 31.65; H, 1.21. Found: C, 31.88; H, 1.35.
IR (neat, cm^{-1}): 2970, 1740, 1365, 1217.

2,4,6-Trichlorophenyl 6-(trifluoromethyl)pyridine-2-sulfonate (4e)



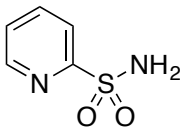
4e

According to General Procedure B, 2-bromo-6-(trifluoromethyl)pyridine (226 mg, 20 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), and TCPC (175 µL, 1 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **4e** as a tan solid (first run: 236.7 mg, 58%; second run: 226 mg, 56%).

M.p. (°C): 110 – 113.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.33 – 8.29 (m, 1H), 8.26 (tt, J = 7.8, 0.6 Hz, 1H), 8.03 (dt, J = 7.8, 0.7 Hz, 1H), 7.36 (d, J = 0.6 Hz, 2H).
^{13}C NMR (126 MHz, Chloroform-d): δ 154.9, 149.7, 149.4, 149.1, 148.8, 142.4, 140.6, 133.6, 130.6, 129.4, 126.4, 126.4, 125.2, 125.2, 125.2, 125.1, 121.6, 119.4.
Elemental Analysis: Anal. calcd. for $C_{12}H_5Cl_3F_3NO_3S$: C, 35.45; H, 1.24. Found: C, 35.72; H, 1.45.
IR (neat, cm^{-1}): 1739, 1561, 1444, 1404, 1330, 1220, 1191, 1142, 1106, 995, 881, 865, 834, 792, 741, 727, 672, 648, 597.

Preparation and Characterization of Compounds in Scheme 3

Pyridine-2-sulfonamide (8a)

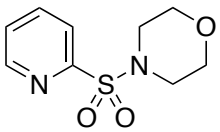


8a

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with 56% ammonium hydroxide (14.5 M, 2 mL, 29 mmol). Diverging from the general procedure, only 2 mL THF were used, and the reaction mixture was stirred in a 60 °C oil bath for only 1 h. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 5% MeOH/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **8a** as a white solid (first run: 145.7 mg, 92%; second run: 128.6 mg, 81%).

M.p. (°C): 144 – 147.
^{1}H-NMR (500 MHz, Methanol-d4): δ 8.68 (ddd, J = 4.7, 1.7, 1.0 Hz, 1H), 8.10 – 7.95 (m, 2H), 7.60 (ddd, J = 7.2, 4.7, 1.5 Hz, 1H).
^{13}C NMR (126 MHz, Methanol-d4): δ 160.9, 150.8, 139.7, 127.9, 122.0.
Elemental Analysis: Anal. calcd. for $C_5H_6N_2O_2S$: C, 37.97; H, 3.82. Found: C, 38.13; H, 3.82.
IR (neat, cm^{-1}): 2487, 2263, 1738, 1582, 1428, 1335, 1290, 1186, 1162, 1151, 1109, 1088, 1043, 998, 865, 836, 785, 734, 607.

4-(Pyridin-2-ylsulfonyl)morpholine (8b)

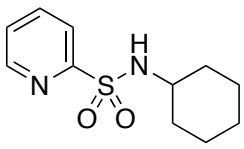


8b

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with morpholine (175 µL, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8b** as a white solid (first run: 225 mg, 98%; second run: 228.5 mg, quant.).

M.p. (°C): 70 – 73.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.78 – 8.63 (m, 1H), 7.97 – 7.85 (m, 2H), 7.51 (ddd, J = 5.6, 4.7, 3.4 Hz, 1H), 3.78 – 3.66 (m, 4H), 3.35 – 3.24 (m, 4H).
^{13}C NMR (126 MHz, Chloroform-d): δ 156.0, 150.2, 138.1, 126.9, 123.3, 66.5, 46.7.
Elemental Analysis: Anal. calcd. for $C_9H_{12}N_2O_3S$: C, 47.36; H, 5.30. Found: C, 47.38; H, 5.19.
IR (neat, cm^{-1}): 1738, 1344, 1258, 1217, 1176, 1114, 1088, 1071, 946, 796, 760, 706, 612.

***N*-Cyclohexylpyridine-2-sulfonamide (8c)**



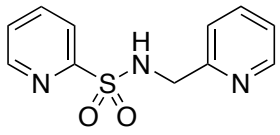
8c

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with cyclohexylamine (230 µL, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8c**

as a white solid (first run: 222.4 mg, 93%; second run: 198.1 mg, 82%).

M.p. (°C): 91 – 93.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.01 (dt, J = 7.9, 1.1 Hz, 1H), 7.90 (td, J = 7.7, 1.7 Hz, 1H), 7.48 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 5.27 (d, J = 7.5 Hz, 1H), 3.22 (dddd, J = 9.8, 7.6, 5.9, 3.9 Hz, 1H), 1.79 – 1.67 (m, 2H), 1.66 – 1.54 (m, 2H), 1.51 – 1.42 (m, 1H), 1.28 – 0.99 (m, 5H).
^{13}C NMR (126 MHz, Chloroform-d): δ 158.6, 150.1, 138.1, 126.6, 122.0, 53.3, 33.9, 25.2, 24.7.
Elemental Analysis: Anal. calcd. for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71. Found: C, 54.93; H, 6.58.
IR (neat, cm^{-1}): 2933, 1738, 1583, 1448, 1427, 1365, 1329, 1217, 1173, 1127, 1082, 996, 888, 780, 737, 623.

N-(Pyridin-2-ylmethyl)pyridine-2-sulfonamide (8d)

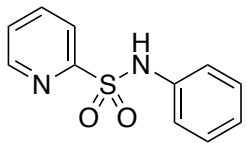


8d

According to General Procedure B, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with pyridin-2-ylmethanamine (206 µL, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 10% MeOH/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **8d** as a slightly-greenish brown solid (first run: 210 mg, 84%; second run: 235.2 mg, 94%).

M.p. (°C): 123 – 126.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.60 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.39 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.94 (dt, J = 7.9, 1.1 Hz, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.58 (td, J = 7.7, 1.8 Hz, 1H), 7.40 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.11 (ddd, J = 7.7, 4.9, 1.1 Hz, 1H), 7.08 – 7.03 (m, 1H), 4.44 (d, J = 6.4 Hz, 2H).
^{13}C NMR (126 MHz, Chloroform-d): δ 157.7, 155.6, 150.1, 149.0, 138.0, 136.9, 126.5, 122.61, 122.2, 122.1, 48.2.
Elemental Analysis: Anal. calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45. Found: C, 53.26; H, 4.46.
IR (neat, cm^{-1}): 1739, 1596, 158, 1482, 1430, 1365, 1329, 1217, 1170, 1114, 1088, 993, 828.

N-Phenylpyridine-2-sulfonamide (8e)[7]



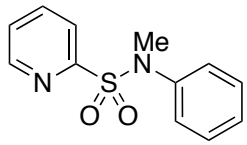
8e

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with aniline (185 µL, 2 mmol) and LHMDS solution (2 mL, 1.0 M, 2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8e** as a white solid (first run: 183 mg, 78%; second run: 158.4 mg, 68%).

[7] *N*-Phenylpyridine-2-sulfonamide has been previously reported and characterized: García-Rubia, A.; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10927-10931.

M.p. (°C): 172 – 175. (Lit. 170 – 172.)
^{1}H-NMR (500 MHz, Methanol-d4): δ 8.65 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 7.98 – 7.88 (m, 2H), 7.54 (ddd, J = 7.4, 4.7, 1.4 Hz, 1H), 7.22 – 7.11 (m, 4H), 7.06 – 7.00 (m, 1H).
^{13}C NMR (126 MHz, Methanol-d4): δ 158.1, 151.1, 139.5, 138.6, 130.0, 128.3, 125.8, 124.0, 122.5.
Elemental Analysis: Anal. calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30. Found: C, 56.38; H, 4.43.

***N*-methyl-*N*-phenylpyridine-2-sulfonamide (8f)[8]**

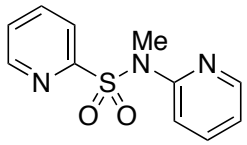


8f

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate 4**a** (339 mg, 1 mmol) was reacted with *N*-methylaniline (130 µL, 1.2 mmol) and LHMDS solution (1.2 mL, 1.0 M, 1.2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 100% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **8f** as a dark yellow solid (first run: 239.1 mg, 96%; second run: 227.3 mg, 92%).

M.p. (°C): 92 – 95. (Lit. 100 – 102.)
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.73 (ddd, J = 4.7, 1.7, 0.8 Hz, 1H), 7.78 (td, J = 7.8, 1.7 Hz, 1H), 7.67 (dt, J = 7.9, 1.0 Hz, 1H), 7.47 (ddd, J = 7.7, 4.7, 1.2 Hz, 1H), 7.28 – 7.14 (m, 5H), 3.47 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-d): δ 156.7, 150.0, 141.2, 137.8, 129.1, 127.5, 127.0, 126.8, 123.2, 40.0.
Elemental Analysis: Anal. calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87. Found: C, 57.76; H, 4.92.

***N*-methyl-*N*-(pyridin-2-yl)pyridine-2-sulfonamide (8g)**



8g

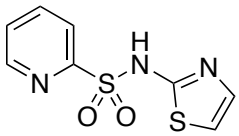
According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with *N*-methylpyridin-2-amine (125 µL, 1.2 mmol) and LHMDS solution (1.2 mL, 1.0 M, 1.2 mmol). The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 10% EtOAc/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **8g** as an orange solid (first run: 224.6, 90%; second run: 234.3 mg, 94%).

M.p. (°C): 71 – 73.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.56 (dt, J = 4.7, 1.3 Hz, 1H), 8.17 (ddt, J = 4.8, 1.7, 0.8 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.62 – 7.53 (m, 2H), 7.42 – 7.36 (m, 1H), 7.01 – 6.95 (m, 1H), 3.42 (s, 2H).

[8] *N*-Methyl-*N*-phenylpyridine-2-sulfonamide has been previously reported and characterized: García-Rubia, A.'; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10927-10931.

^{13}C NMR (126 MHz, Chloroform-d): δ 156.0, 153.4, 150.0, 147.7, 137.8, 137.6, 126.9, 122.8, 120.6, 118.9, 36.2.
Elemental Analysis: Anal. calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45. Found: C, 52.70; H, 4.47.
IR (neat, cm^{-1}): 1738, 1573, 1471, 1429, 1365, 1345, 1311, 1229, 1217, 1172, 1159, 1087, 1067, 986, 895, 779, 771, 748, 736, 709, 624, 593.

***N*-(thiazol-2-yl)pyridine-2-sulfonamide (8h)**



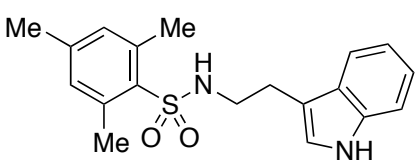
8h

According to General Procedure C, 2,4,6-trichlorophenyl pyridine-2-sulfonate **4a** (339 mg, 1 mmol) was reacted with 2-aminothiazole (201 mg, 2 mmol) and LHMDS solution (2 mL, 1.0 M, 2 mmol). Diverging from the general procedure, the crude product was loaded onto a short silica plug that had been pre-flushed with dichloromethane. The plug was flushed with 100 mL dichloromethane, collected as a first fraction, and then 100 mL methanol, collected as a second fraction. The methanol fraction was concentrated and the concentrate was recrystallized from methanol, filtered, washed with cold methanol, and dried to afford **8h** as a red-brown solid (first run: 154.3 mg, 64%; second run: 135.9 mg, 61%).

Decomposition point (°C): 170.
^{1}H-NMR (500 MHz, DMSO-d6): δ 8.63 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.02 (td, J = 7.7, 1.8 Hz, 1H), 7.94 (dt, J = 7.9, 1.1 Hz, 1H), 7.58 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.27 (d, J = 4.6 Hz, 1H), 6.87 (d, J = 4.6 Hz, 1H).
^{13}C NMR (126 MHz, DMSO-d6): δ 170.3, 159.0, 150.0, 138.4, 126.7, 124.2, 120.8, 108.8.
Elemental Analysis: Anal. calcd. for $C_8H_7N_3O_2S_2$: C, 39.82; H, 2.92. Found: C, 39.53; H, 3.00.
IR (neat, cm^{-1}): 1738, 1495, 1428, 1365, 1299, 1217, 1162, 11512, 1112, 929, 851, 739, 725, 629, 620, 592.

Preparation and Characterization of Compounds in Scheme 4

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2,4,6-trimethylbenzenesulfonamide (9a)**

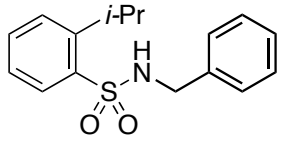


9a

According to General Procedure D, 2-bromo-1,3,5-trimethylbenzene (153 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and tryptamine (321 mg, 2 mmol). Diverging from the general procedure, tryptamine was added as a solid directly to the sulfonyl chloride solution by quickly removing the cap of the reaction vessel rather than via needle/syringe. The mixture was allowed to stir for 24 h after the addition of tryptamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 70% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **9a** as a tan solid (first run: 170 mg, 50%; second run: 183.2 mg, 54%).

M.p. (°C): 136 – 138.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.35 – 8.29 (bs, 1H), 7.39 – 7.34 (m, 2H), 7.20 (ddd, J = 8.2, 7.0, 1.0 Hz, 1H), 7.05 (ddd, J = 7.8, 7.0, 0.9 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 6.86 (s, 2H), 4.65 (t, J = 6.1 Hz, 1H), 3.23 (q, J = 6.5 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.49 (s, 6H), 2.30 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-d): δ 142.1, 138.9, 136.5, 133.1, 131.9, 126.8, 122.8, 122.1, 119.3, 118.3, 111.5, 111.2, 42.5, 25.2, 22.7, 20.9.
IR (neat, cm^{-1}): 3398, 3294, 1460, 1320, 1297, 1154, 1082, 1061, 1010, 851, 818, 746, 740, 654.
HRMS ($C_{19}H_{22}N_2O_2S$): Calcd. $[M+H]^+$: 343.1475. Found: 343.1475.

***N*-Benzyl-2-isopropylbenzenesulfonamide (9b)**



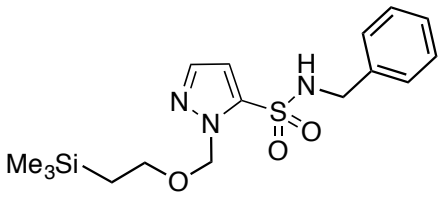
9b

According to General Procedure D, 1-bromo-2-isopropylbenzene (153 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and benzylamine (220 µL, 2 mmol). The mixture was allowed to stir for 18 h after the addition of benzylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate by UV lamp) to afford **9b** as a white solid (first run: 173.1 mg, 60%; second run: 151.5 mg, 52%).

M.p. (°C): 109 – 110.
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.99 (dd, J = 8.0, 1.4 Hz, 1H), 7.55 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.50 (dd, J = 7.9, 1.4 Hz, 1H), 7.32 – 7.24 (m, 4H), 7.19 – 7.16 (m, 2H), 4.74 (t, J = 6.2 Hz, 1H), 4.14 (d, J = 6.1 Hz, 2H), 3.81 (hept, J = 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 6H).
^{13}C NMR (126 MHz, Chloroform-d): δ 148.6, 136.9, 136.4, 133.3, 129.6, 128.9, 128.1, 128.1, 128.1, 126.0, 47.5, 29.6, 24.2.
Elemental Analysis: Anal. calcd. for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62. Found: C, 66.45; H, 6.45.

IR (neat, cm^{-1}): 3304, 1495, 1438, 1420, 1364, 1316, 1153, 1118, 1082, 1068, 1055, 1027, 825, 761, 729, 695, 688, 597, 573, 563.

***N*-Benzyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-5-sulfonamide (9c)**

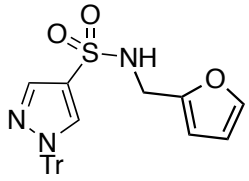


9c

According to General Procedure D, 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (130 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and benzylamine (220 µL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of benzylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 40% EtOAc/hexanes gradient, visualized on TLC plate with $KMnO_4$ stain) to afford **9c** as a clear oil (first run: 114.7 mg, 31%; second run: 106.9 mg, 29%).

^{1}H-NMR (500 MHz, Chloroform-d): δ 7.50 (d, J = 1.9 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.21 – 7.17 (m, 2H), 6.87 (d, J = 1.9 Hz, 1H), 5.69 (s, 2H), 5.43 (t, J = 6.1 Hz, 1H), 4.08 (d, J = 6.1 Hz, 2H), 3.45 – 3.41 (m, 2H), 0.64 – 0.60 (m, 2H), -0.09 (s, 9H).
^{13}C NMR (126 MHz, Chloroform-d): δ 138.8, 138.1, 135.7, 128.8, 128.2, 127.9, 113.1, 79.5, 67.2, 47.9, 17.8, -1.5.
Elemental Analysis: Anal. calcd. for $C_{16}H_{25}N_3O_3SSi$: C, 52.29; H, 6.86. Found: C, 52.54; H, 6.96.
HRMS ($C_{16}H_{25}N_3O_3SSi$): Calcd. $[M+H]^+$: 368.1459. Found: 368.1465.
IR (neat, cm^{-1}): 1738, 1347, 1249, 1160, 1075, 834, 749, 697, 616.

***N*-(Furan-2-ylmethyl)-1-trityl-1*H*-pyrazole-4-sulfonamide (9d)**



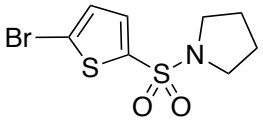
9d

According to General Procedure D, 4-bromo-1-trityl-1*H*-pyrazole (390 mg, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and furfurylamine (180 µL, 2 mmol). Diverging from the general procedure, the reaction tube was put in a -78 °C (dry ice/acetone) bath with magnetic stirring before the addition of TCPC. The bath was allowed to warm overnight (13 h) and then the mixture was stirred at rt for an additional 0.5 h before proceeding with the addition of amine. The mixture was allowed to stir for 2 h after the addition of furfurylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 70% EtOAc/hexanes gradient, visualized on TLC plate by anisaldehyde stain) to afford **9d** as an orange-brown solid (first run: 291.7 mg, 62%; second run: 315 mg, 67%).

M.p. (°C): 175 – 180.
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.84 (dd, J = 0.4 Hz, 1H), 7.78 (dd, J = 0.8, 0.3 Hz, 1H), 7.38 – 7.30 (m, 9H), 7.24 (dt, J = 1.9, 0.5 Hz, 1H), 7.11 – 7.07 (m, 6H), 6.22 (dd, J = 3.2, 1.9 Hz, 1H), 6.12 (dd, J = 3.2, 0.8 Hz, 1H), 4.73 (t, J = 6.0 Hz, 1H), 4.26 – 4.22 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d): δ 149.6, 142.5, 142.0, 138.6, 134.0, 130.0, 128.3, 128.0, 121.1, 110.5, 108.3, 80.0, 40.0.
IR (neat, cm^{-1}): 1445, 1319, 1151, 1104, 869, 745, 700, 640.
HRMS ($C_8H_9N_3O_3S$ – loss of CPh_3 group): Calcd. $[M+H]^+$: 228.0437. Found: 228.0456.

1-((5-Bromothiophen-2-yl)sulfonyl)pyrrolidine (9e)

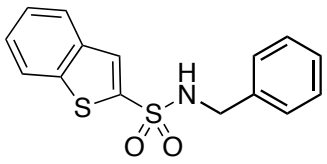


9e

According to General Procedure D, 2,5-dibromothiophene (113 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and pyrrolidine (170 µL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of pyrrolidine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate with UV lamp) to afford **9e** as a slightly orange solid (first run: 255.5 mg, 86%; second run: 245.7 mg, 83%).

M.p. (°C): 67 – 69.
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.30 (dd, J = 4.0, 0.6 Hz, 1H), 7.13 – 7.04 (m, 1H), 3.30 – 3.18 (m, 4H), 1.80 – 1.76 (m, 4H).
^{13}C NMR (126 MHz, Chloroform-d): δ 138.1, 132.4, 130.8, 119.5, 48.5, 25.6.
HRMS ($C_8H_{10}BrNO_2S_2$): Calcd. $[M+H]^+$: 295.9409. Found: 295.9401.
IR (neat, cm^{-1}): 1406, 1337, 1209, 1062, 1017, 1006, 805, 753, 667.

***N*-Benzylbenzo[*b*]thiophene-2-sulfonamide (9f)**

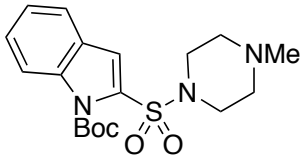


9f

According to General Procedure D, benzo[*b*]thiophene (120 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and benzylamine (220 µL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of benzylamine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 50% EtOAc/hexanes gradient, visualized on TLC plate with UV lamp) to afford **9f** as a pink solid (first run: 238 mg, 78%; second run: 228.8 mg, 75%).

M.p. (°C): 118 – 119.
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.90 – 7.85 (m, 3H), 7.53 – 7.45 (m, 2H), 7.31 – 7.23 (m, 5H), 4.87 (t, J = 6.1 Hz, 1H), 4.27 (d, J = 6.1 Hz, 2H).
^{13}C NMR (126 MHz, Chloroform-d): δ 141.8, 140.8, 137.7, 135.9, 129.7, 128.8, 128.1, 128.0, 127.4, 125.8, 125.6, 122.8, 47.6.
HRMS ($C_{15}H_{13}NO_2S_2$): Calcd. $[M+NH_4]^+$: 321.0726. Found: 321.0737.
IR (neat, cm^{-1}): 3259, 1425, 1333, 1148, 1039, 1022, 1002, 746, 695, 596, 556.

***Tert*-butyl 2-((4-methylpiperazin-1-yl)sulfonyl)-1*H*-indole-1-carboxylate (9g)**

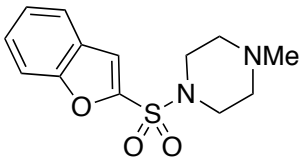


9g

According to General Procedure D, *tert*-butyl 1*H*-indole-1-carboxylate (203 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and 1-methylpiperazine (222 µL, 2 mmol). Diverging from the general procedure, the reaction tube was put in a -78 °C (dry ice/acetone) bath with magnetic stirring before the addition of TCPC. The bath was allowed to warm overnight (14 h) and then the mixture was stirred at rt for an additional 0.5 h before proceeding with the addition of amine. The mixture was allowed to stir for 2 h after the addition of 1-methylpiperazine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 5% MeOH/dichloromethane gradient, visualized on TLC plate with UV lamp) to afford **9g** as a brown solid (first run: 179 mg, 47%; second run: 147.7 mg, 39%).

M.p. (°C): 151 – 154.
^{1}H-NMR (500 MHz, Chloroform-d): δ 8.13 (dt, J = 8.6, 0.8 Hz, 1H), 7.61 (dt, J = 7.9, 1.0 Hz, 1H), 7.45 (ddt, J = 8.2, 7.4, 0.9 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.10 (d, J = 0.8 Hz, 1H), 3.58 – 3.51 (m, 4H), 2.53 (t, J = 4.9 Hz, 4H), 2.36 (s, 3H), 1.73 (d, J = 0.6 Hz, 9H).
^{13}C NMR (126 MHz, Chloroform-d): δ 148.5, 137.5, 135.7, 127.5, 126.0, 123.6, 122.3, 115.8, 115.0, 86.1, 55.0, 46.3, 46.1, 28.1.
Elemental Analysis: Anal. calcd. for $C_{18}H_{25}N_3O_4S$: C, 56.97; H, 6.64. Found: C, 56.71; H, 6.55.
HRMS ($C_{18}H_{25}N_3O_2S$): Calcd. $[M+NH_4]^+$: 380.1639. Found: 380.1624.
IR (neat, cm^{-1}): 2784, 1737, 1446, 1357, 1336, 1318, 1285, 1257, 1217, 1140, 1098, 1068, 844, 821, 753, 717, 619, 588.

1-(Benzofuran-2-ylsulfonyl)-4-methylpiperazine (9h)



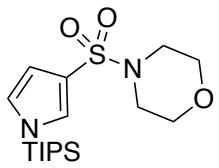
9h

According to General Procedure D, benzofuran (110 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and 1-methylpiperazine (222 µL, 2 mmol). The mixture was allowed to stir for 2 h after the addition of 1-methylpiperazine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 10% MeOH/dichloromethane gradient, visualized on TLC plate by UV lamp) to afford **9h** as a tan solid (first run: 187.5 mg, 67%; second run: 170 mg, 61%).

M.p. (°C): 86 – 91.
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.67 (dt, J = 7.8, 1.0 Hz, 1H), 7.53 (dt, J = 8.4, 0.9 Hz, 1H), 7.45 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.36 (t, J = 0.8 Hz, 1H), 7.33 (tt, J = 7.2, 0.8 Hz, 1H), 3.32 (t, J = 4.9 Hz, 4H), 2.50 (t, J = 5.1 Hz, 4H), 2.28 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-d): δ 155.9, 148.3, 127.8, 125.8, 124.3, 122.9, 113.3, 112.3, 54.1, 45.9, 45.8.

Elemental Analysis: Anal. calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75. Found: C, 55.42; H, 5.66.
IR (neat, cm^{-1}): 1144, 1360, 1282, 1236, 1181, 1150, 950, 925, 866, 793, 782, 737, 725, 645, 620.

4-((1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl)sulfonyl)morpholine (9i)

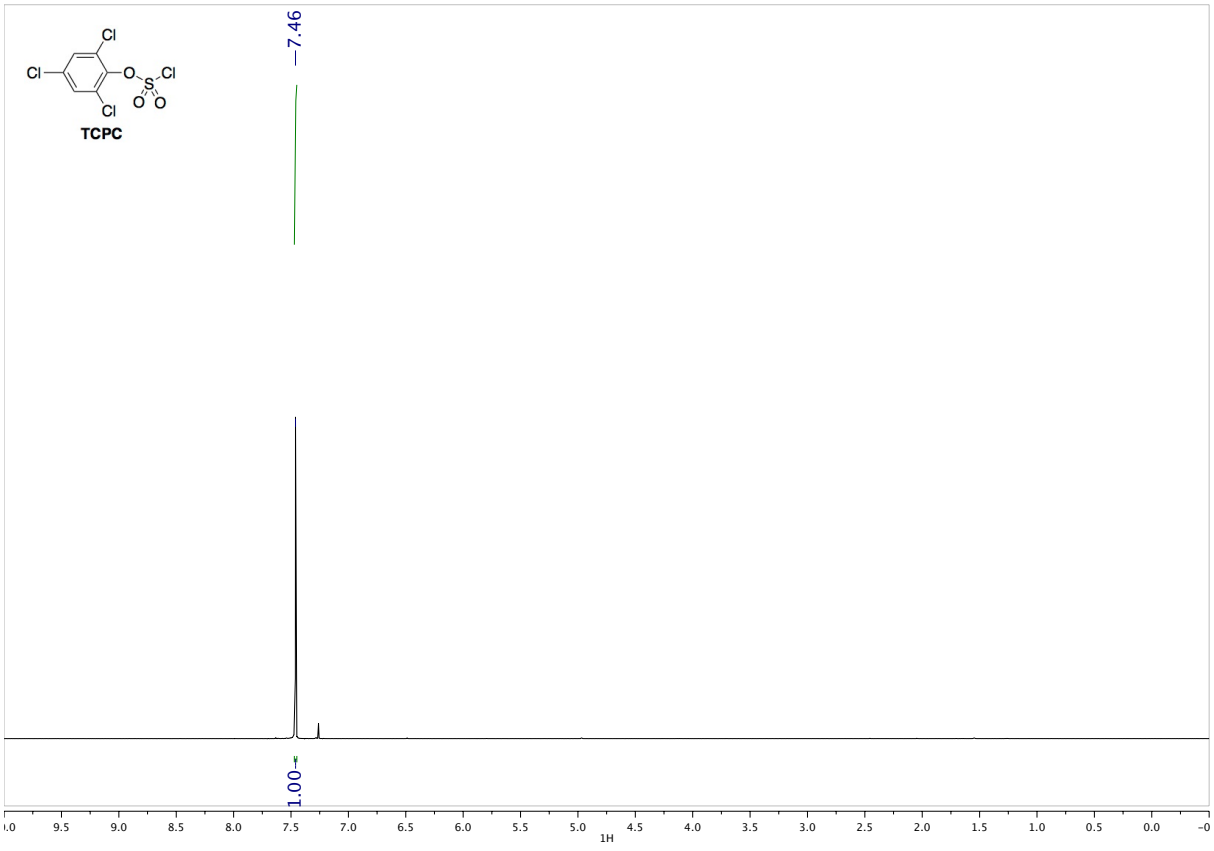


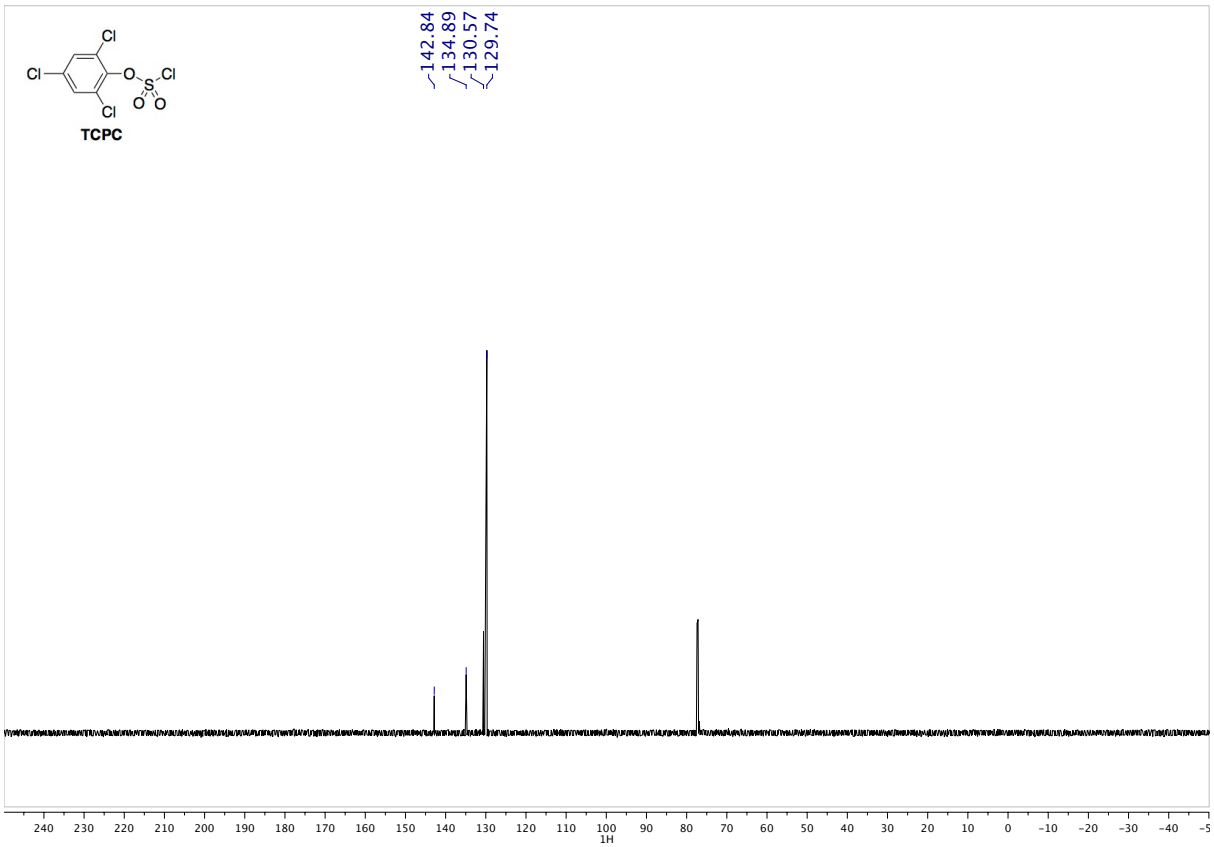
9i

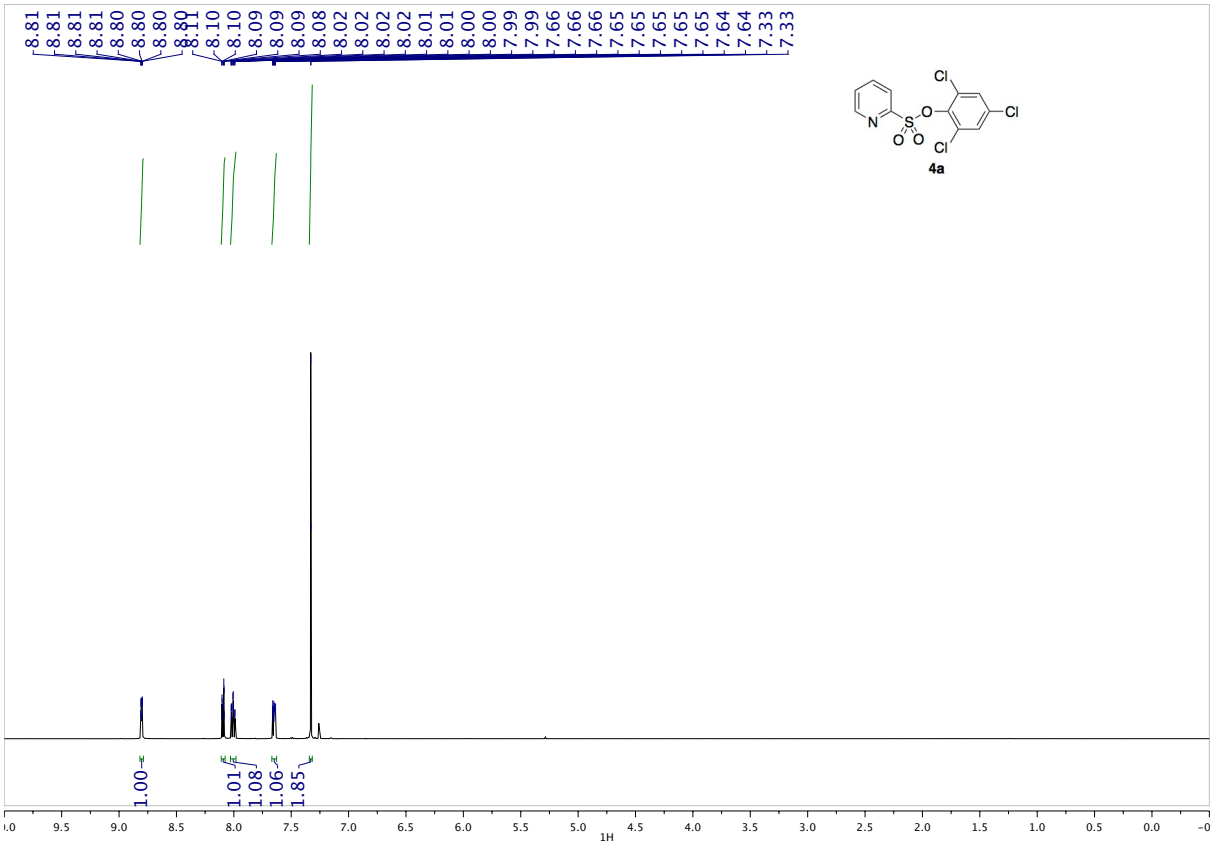
According to General Procedure A, 3-bromo-1-(triisopropylsilyl)-1*H*-pyrrole (270 µL, 1 mmol) was reacted sequentially with *n*-butyllithium solution (400 µL, 2.5 M, 1 mmol), $ZnCl_2$ solution (530 µL, 1.9 M, 1 mmol), TCPC (175 µL, 1 mmol), and morpholine (175 µL, 2 mmol). Diverging from the general procedure, the reaction tube was put in a -78 °C (dry ice/acetone) bath with magnetic stirring before the addition of TCPC. The bath was allowed to warm overnight (14 h) and then the mixture was stirred at rt for an additional 0.5 h before proceeding with the addition of amine. The mixture was allowed to stir for 2 h after the addition of morpholine. The crude product was purified by silica gel chromatography with a Biotage instrument (silica-packed 50 g SNAP column, 0 – 70% EtOAc/hexanes gradient, visualized on TLC plate with $KMnO_4$ stain) to afford **9i** as a brown solid (first run: 155.8 mg, 42%; second run: 122.9 mg, 31%).

M.p. (°C): 74 – 79.
^{1}H-NMR (500 MHz, Chloroform-d): δ 7.21 (dd, J = 2.2, 1.4 Hz, 1H), 6.80 (dd, J = 2.9, 2.2 Hz, 1H), 6.51 (dd, J = 2.9, 1.4 Hz, 1H), 3.78 – 3.75 (m, 4H), 2.99 – 2.95 (m, 4H), 1.47 (h, J = 7.5 Hz, 3H), 1.10 (d, J = 7.5 Hz, 18H).
^{13}C NMR (126 MHz, Chloroform-d): δ 128.7, 126.1, 119.3, 110.6, 66.4, 46.2, 17.8, 11.7.
Elemental Analysis: Anal. calcd. for $C_{17}H_{32}N_2O_3SSi$: C, 54.80; H, 8.66. Found: C, 54.50; H, 8.50.
IR (neat, cm^{-1}): 2948, 2863, 1509, 1455, 1339, 1326, 1292, 1260, 1147, 1118, 1090, 1070, 1021, 994, 949, 935, 882, 848, 695, 653, 614.

^{1}H and ^{13}C NMR Spectra



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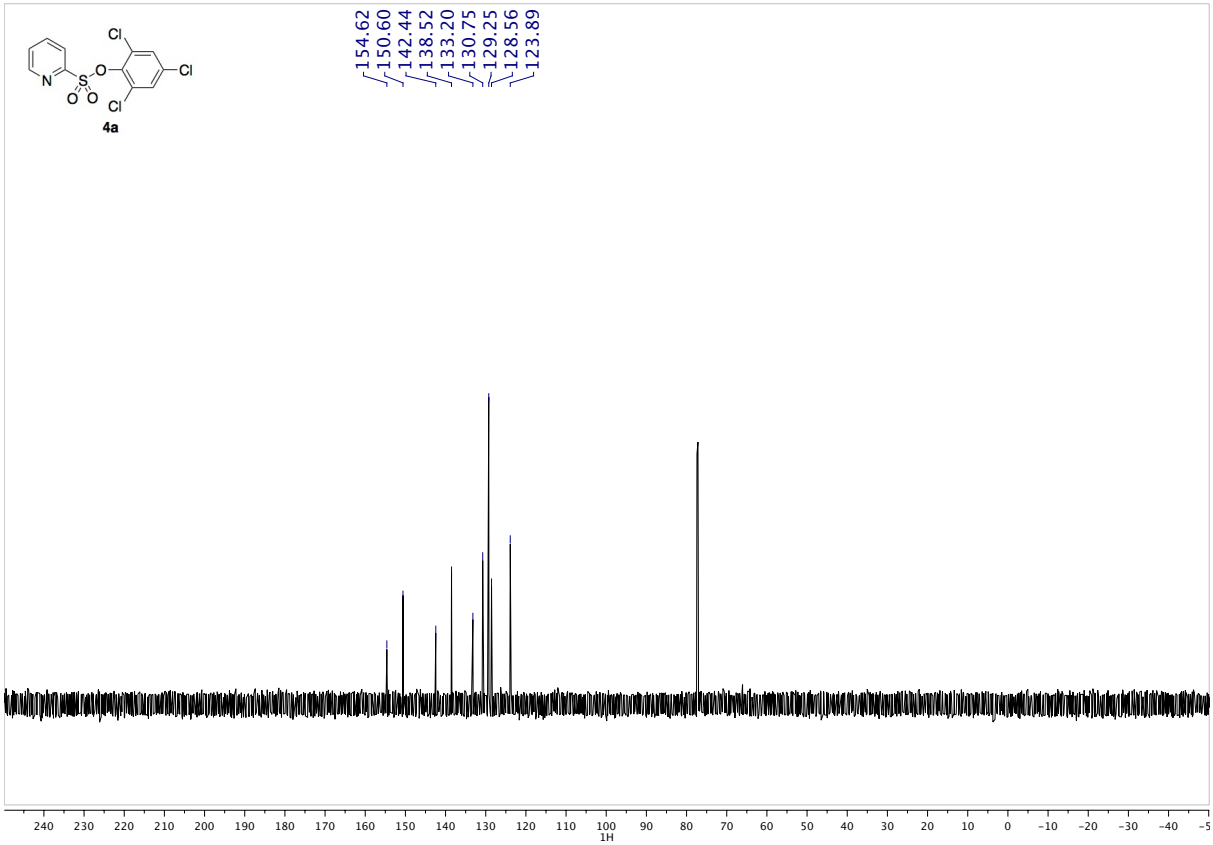
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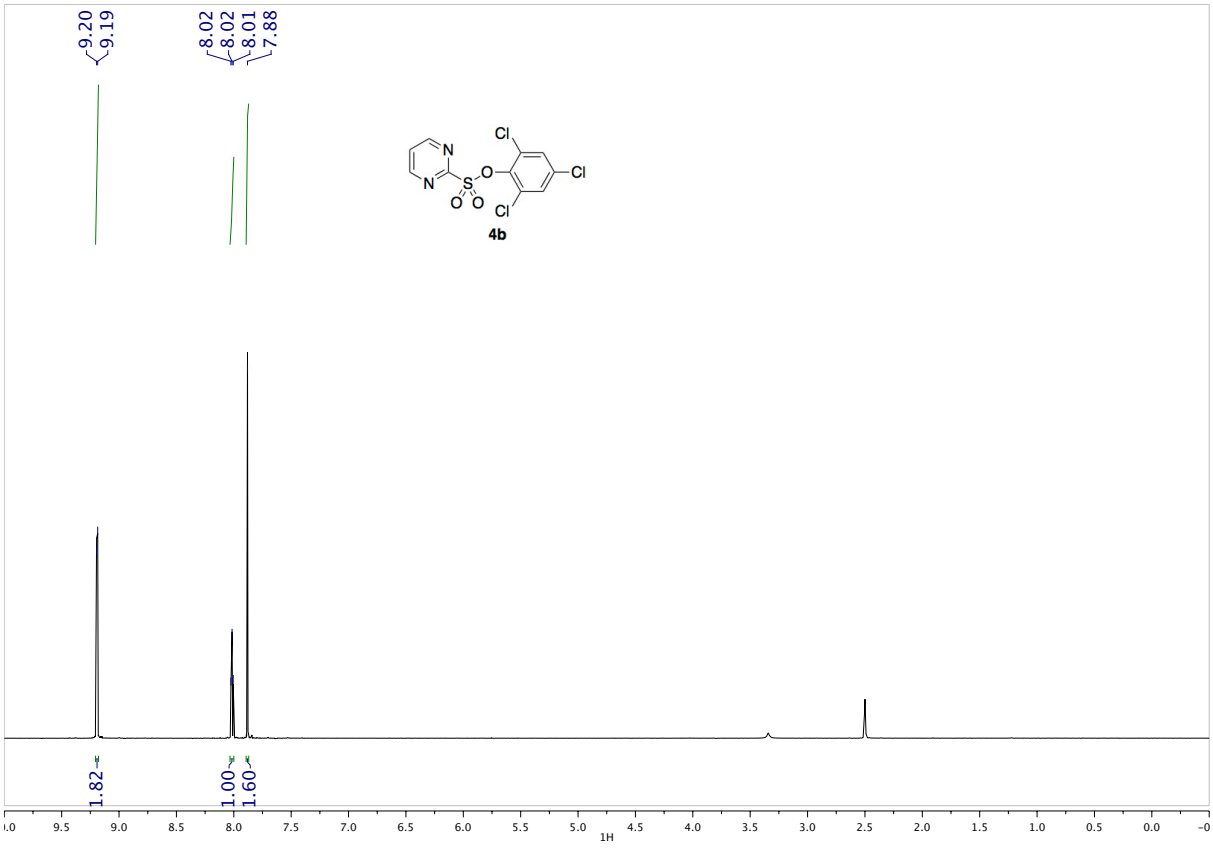
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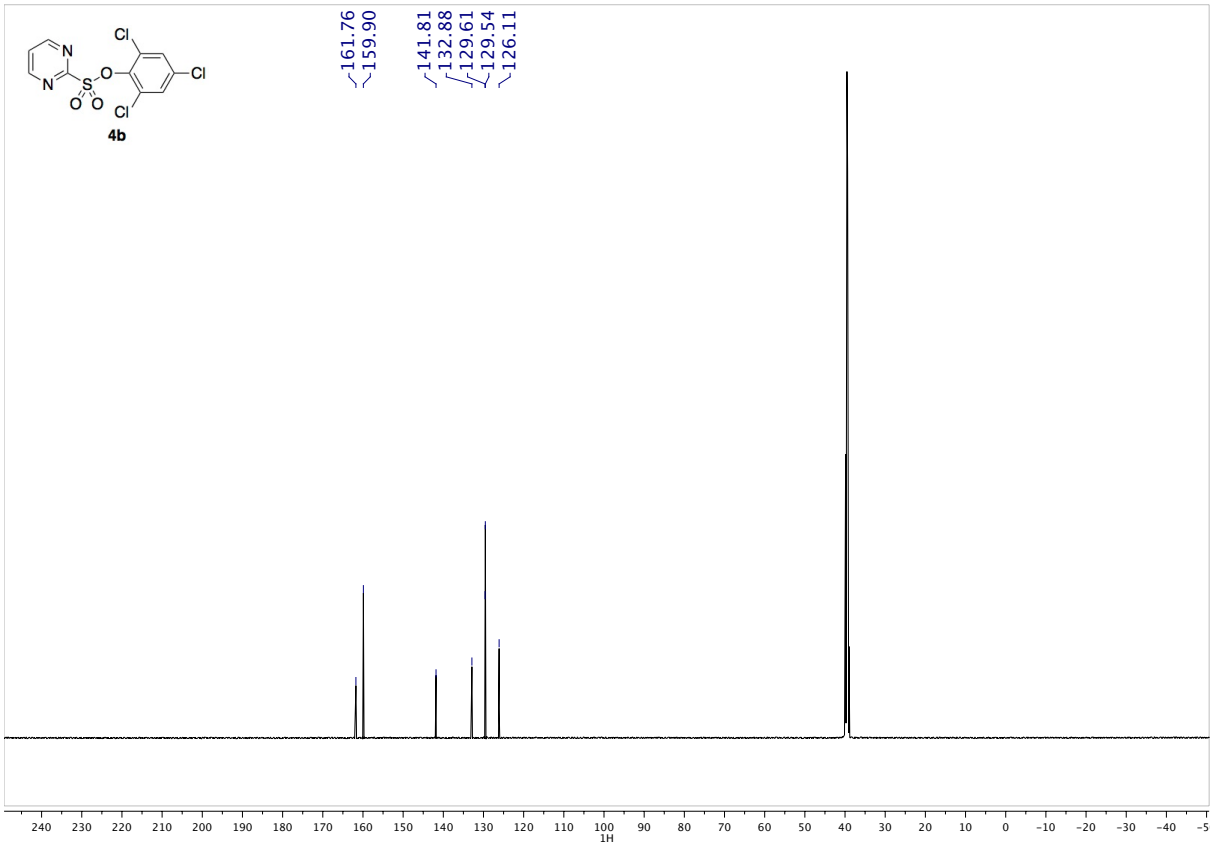
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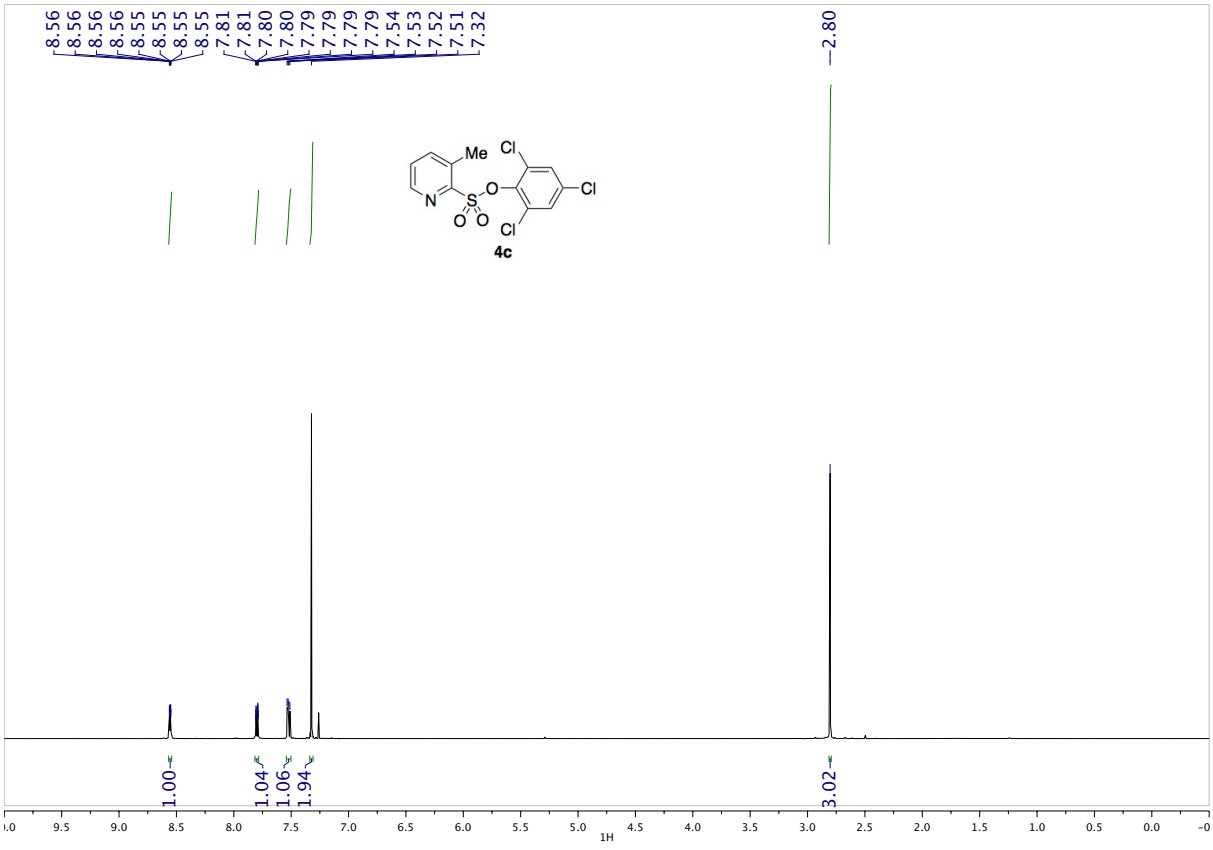
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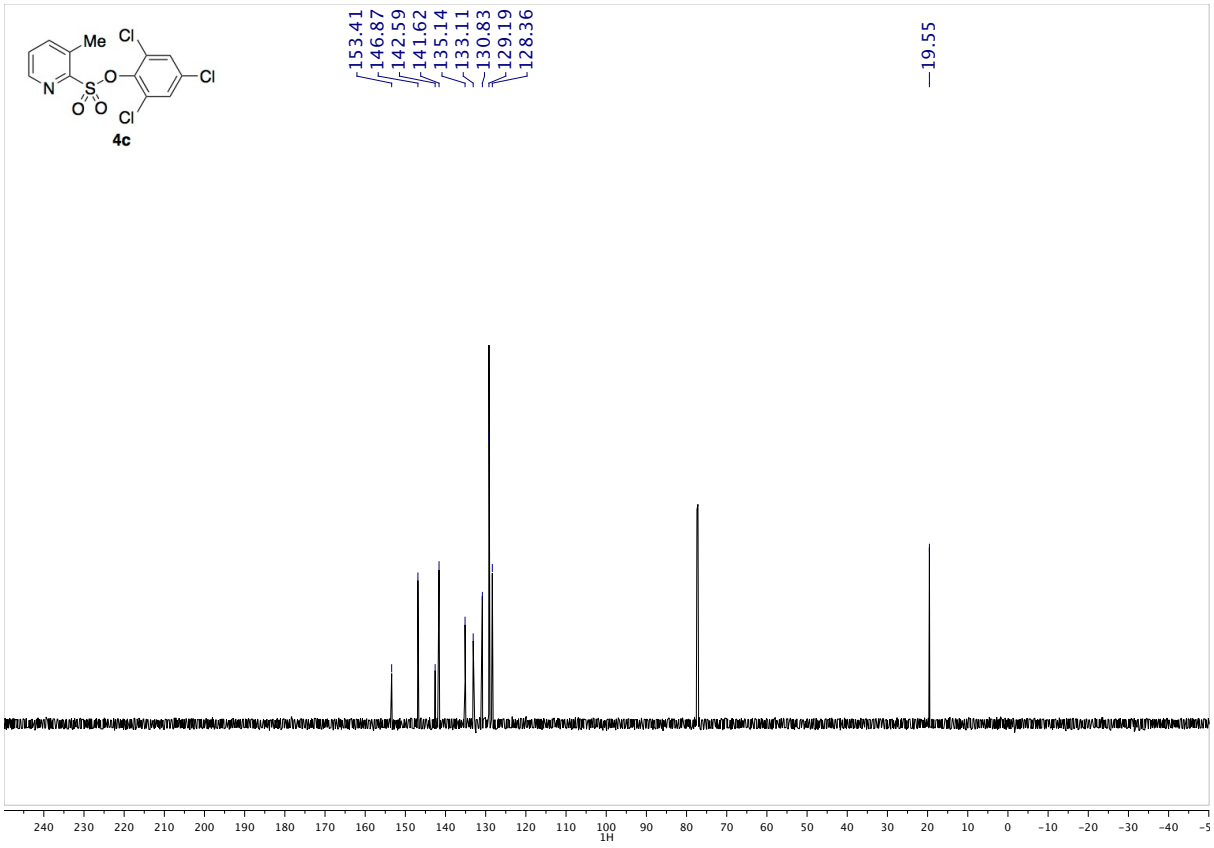
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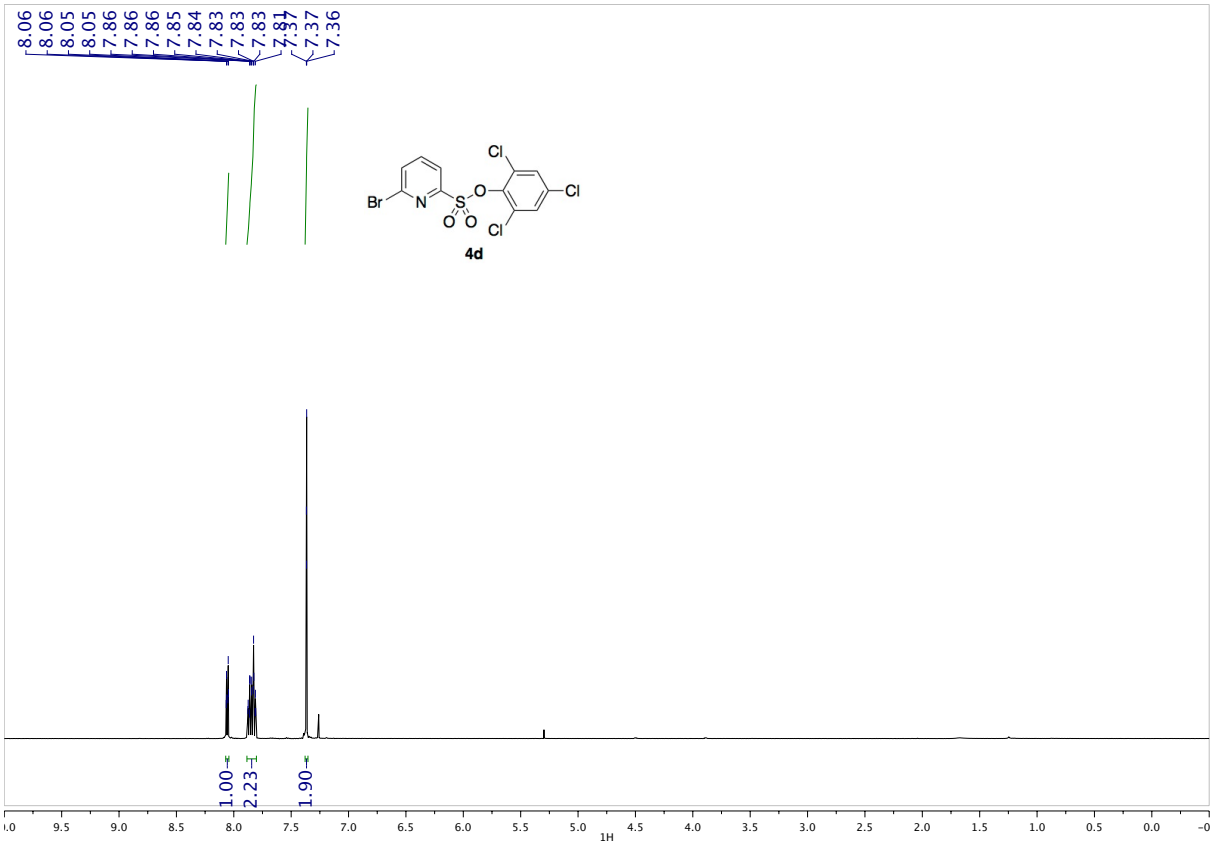
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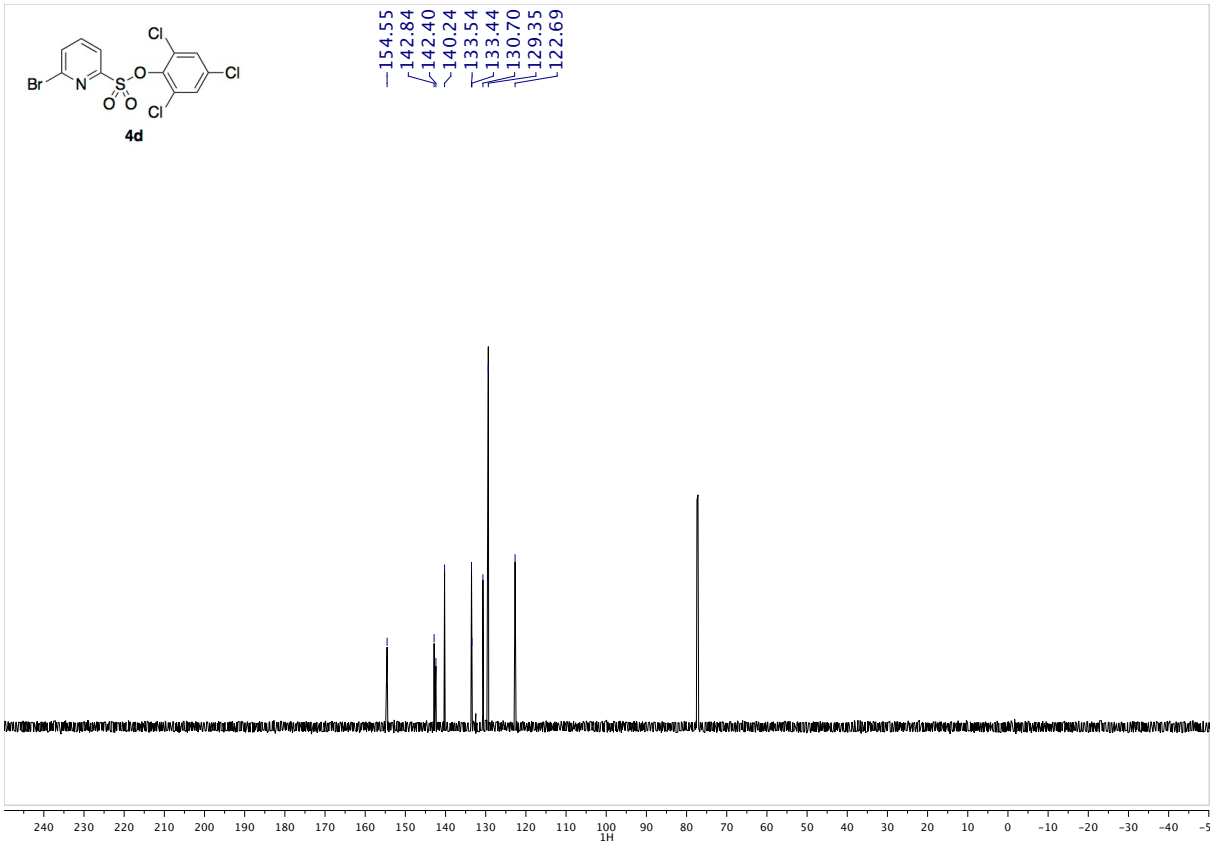
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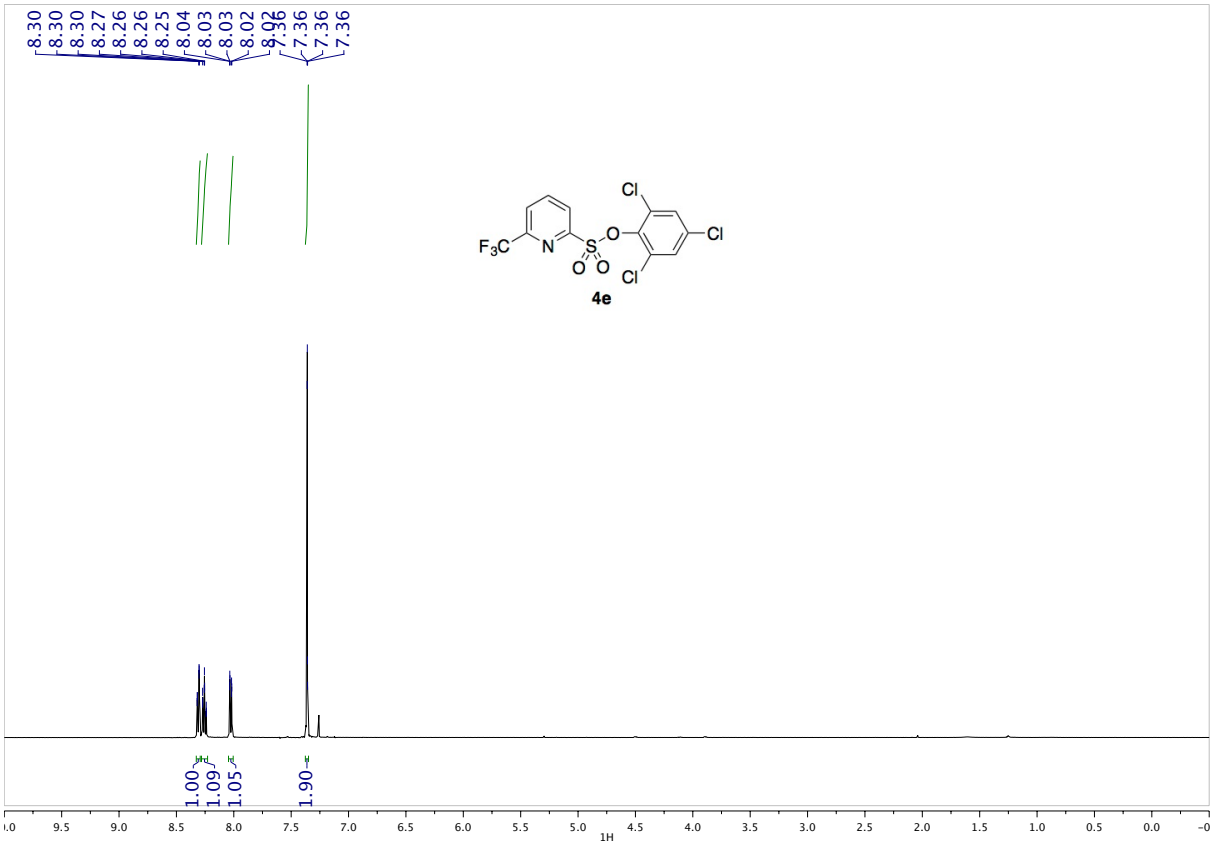
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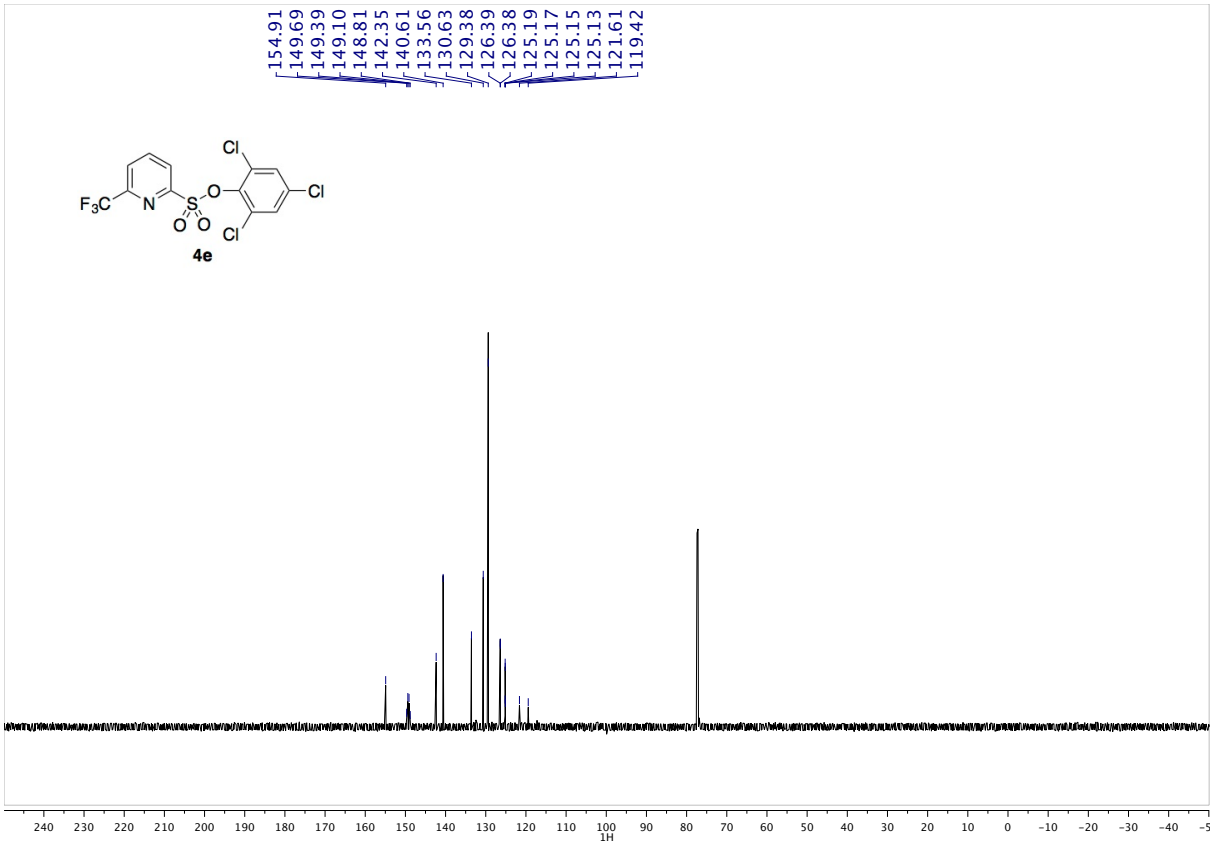
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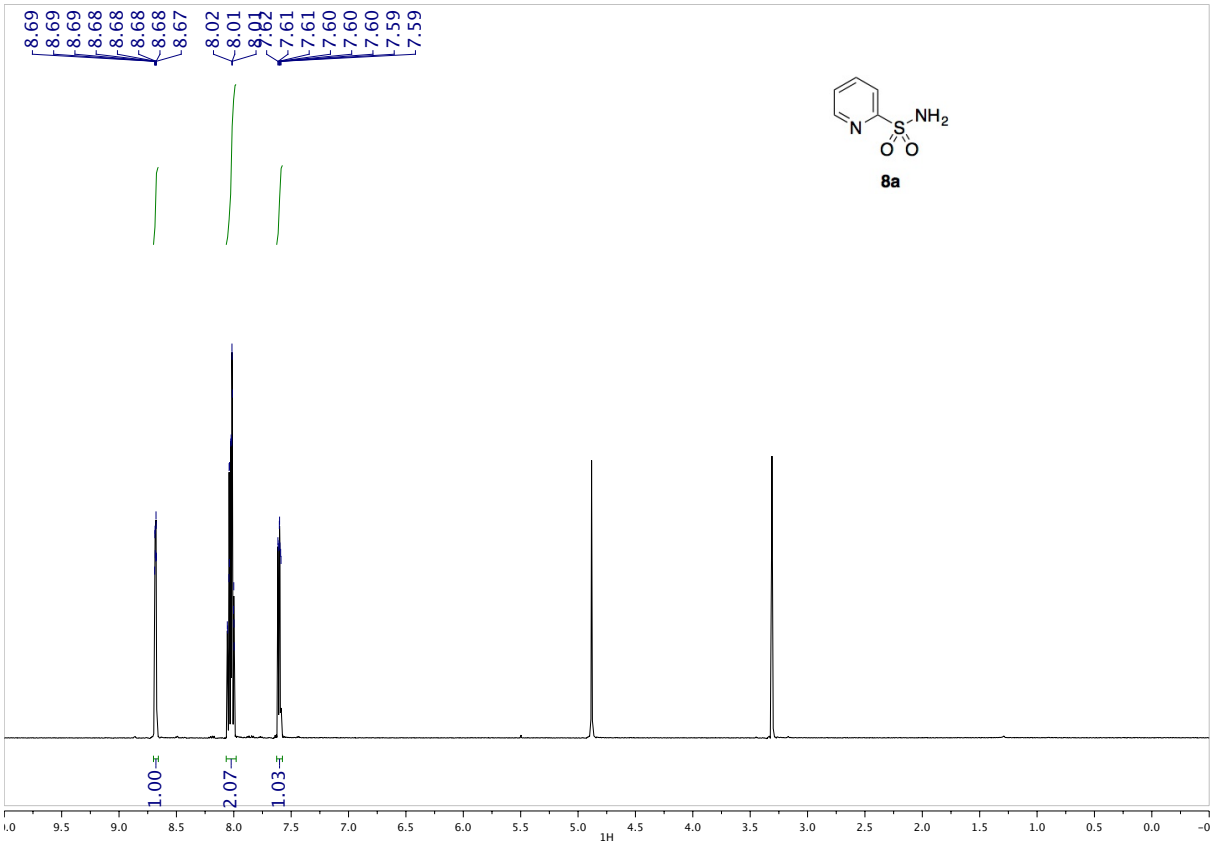
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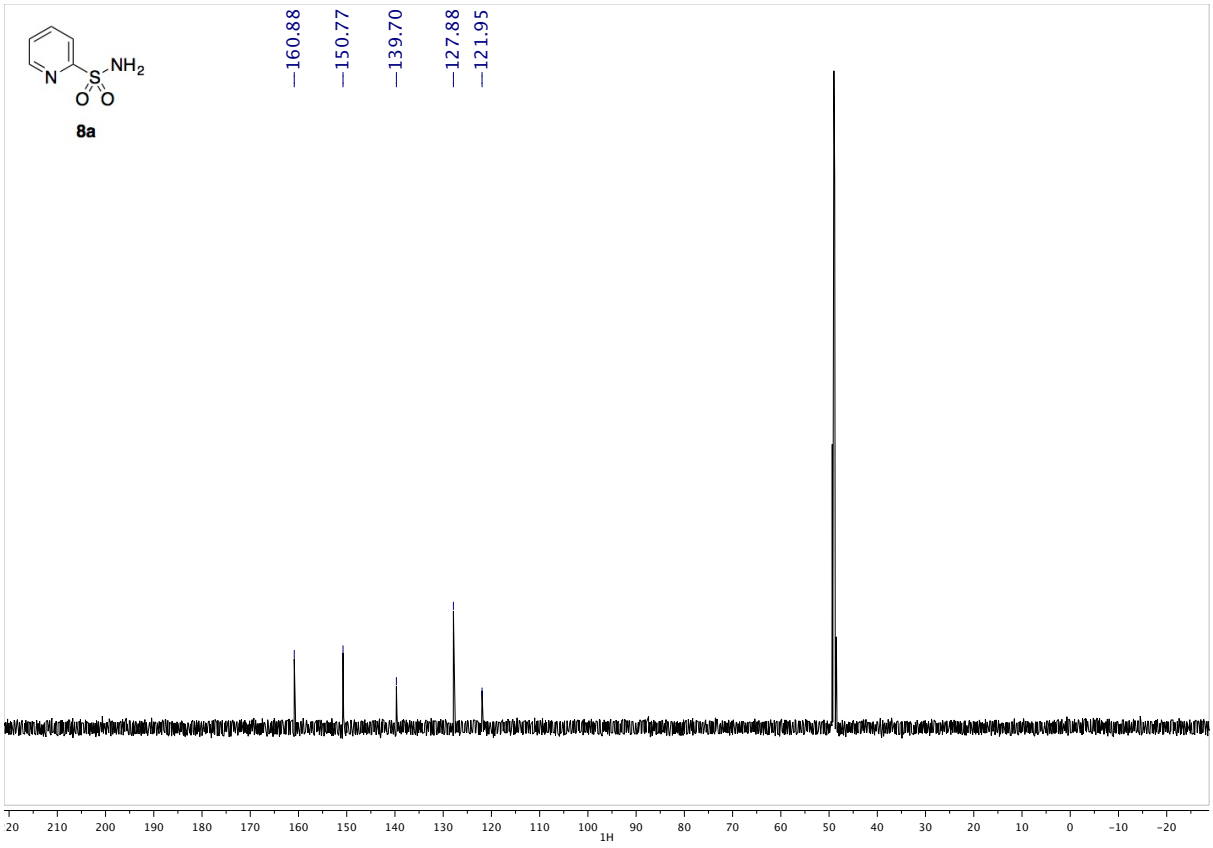
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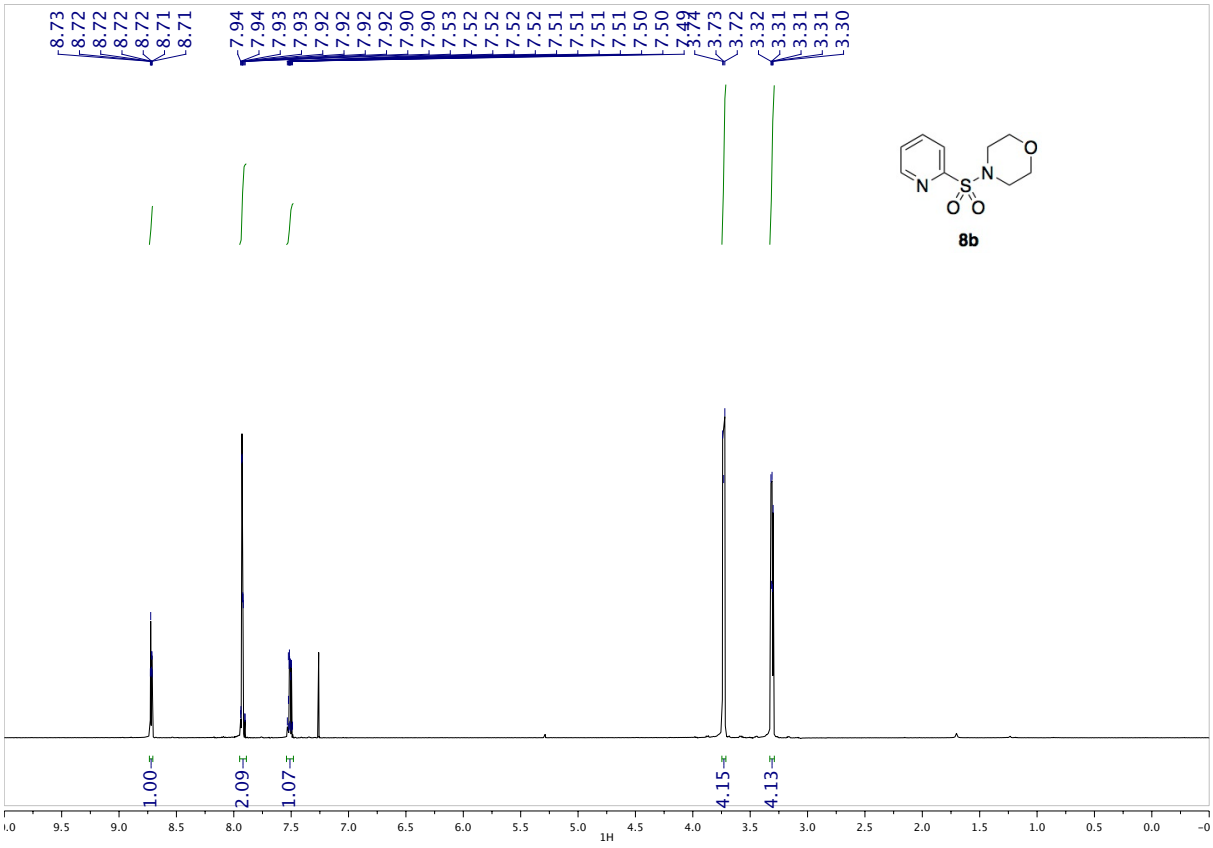
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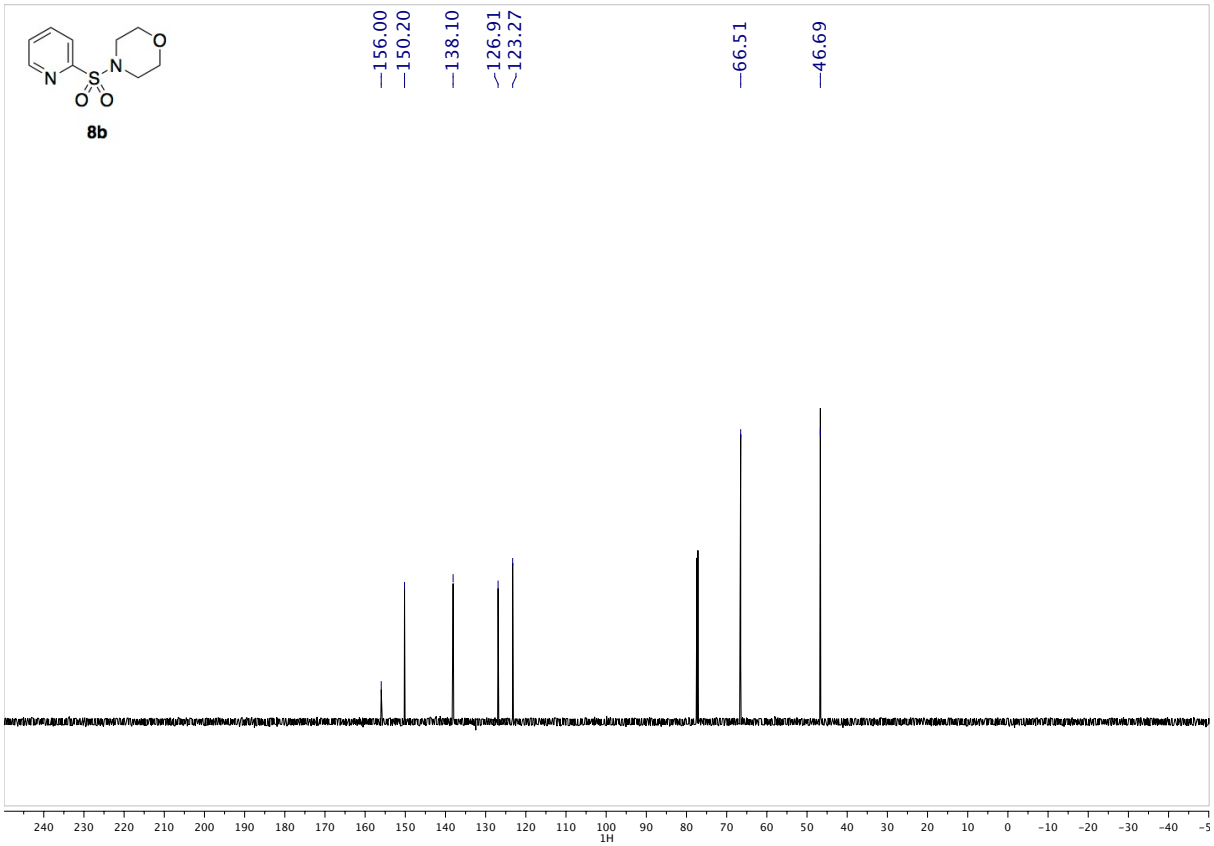
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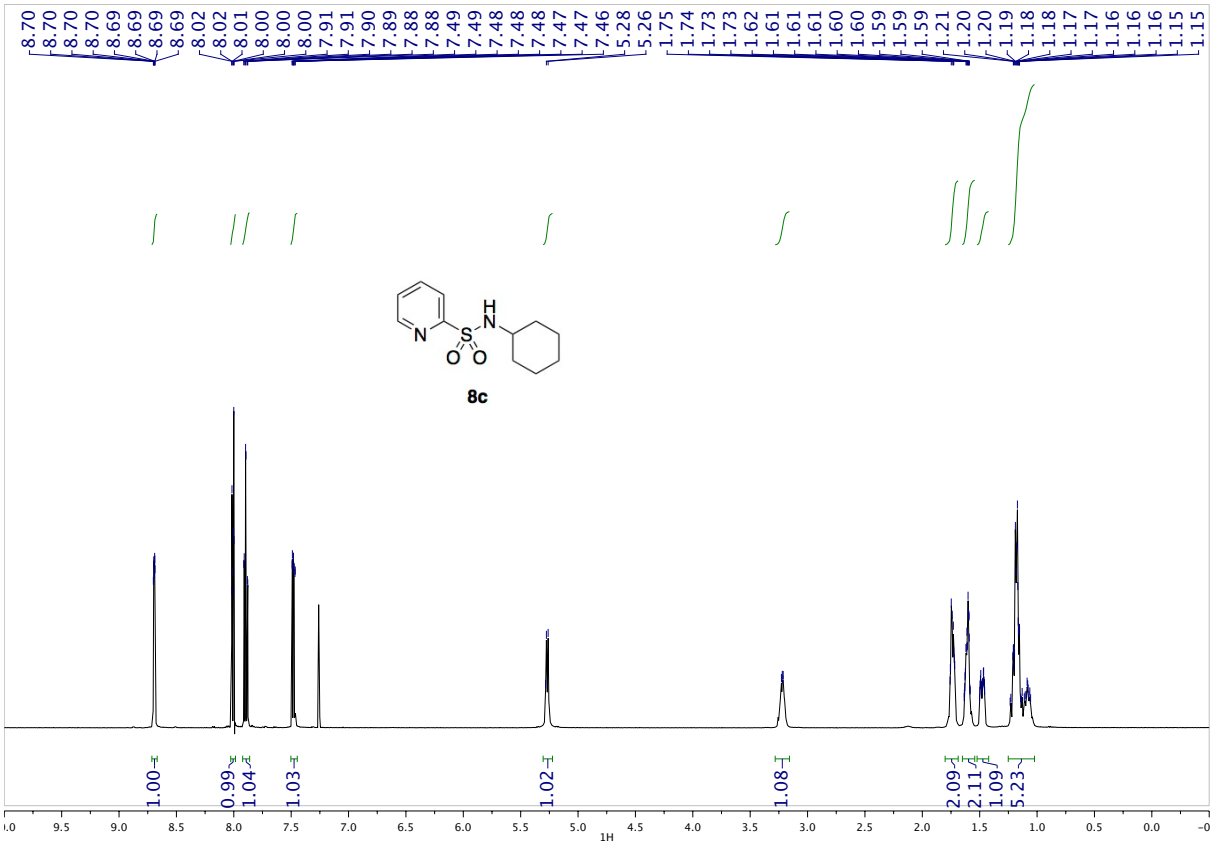
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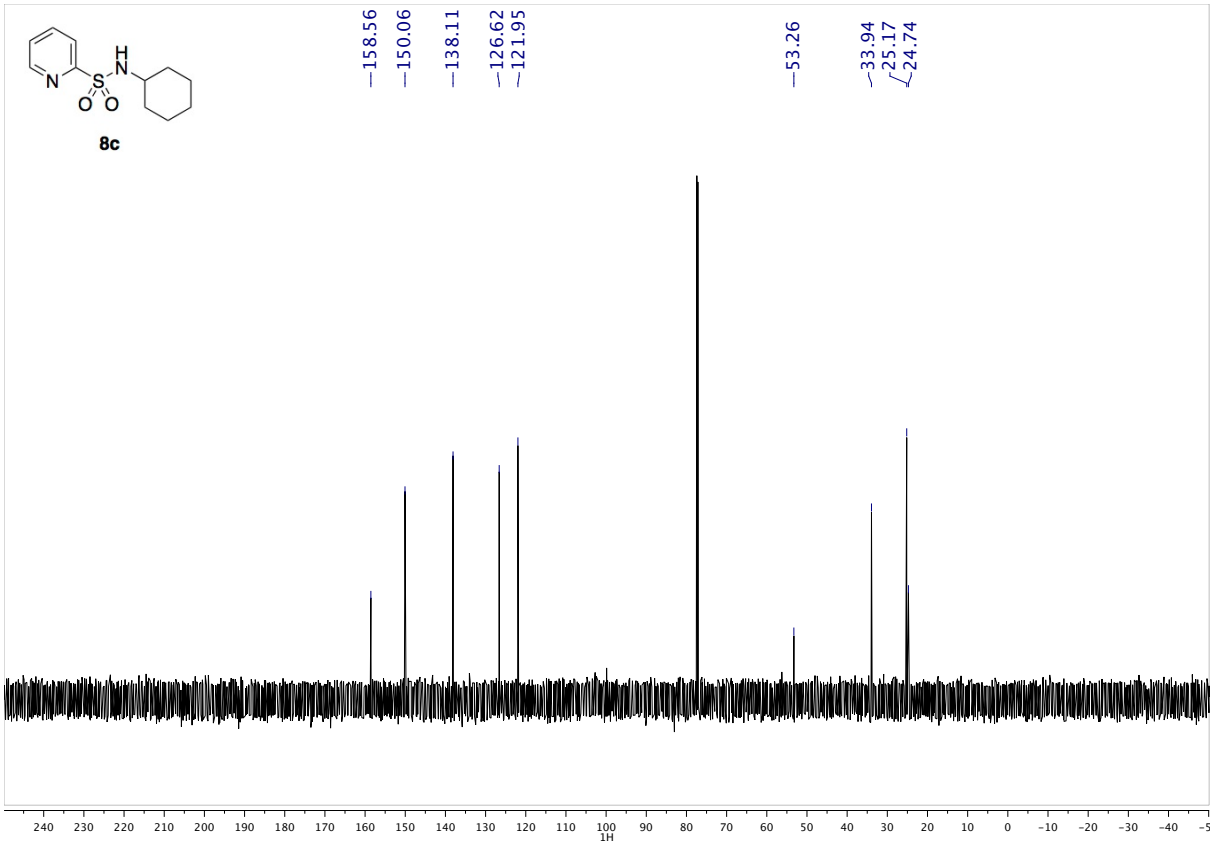
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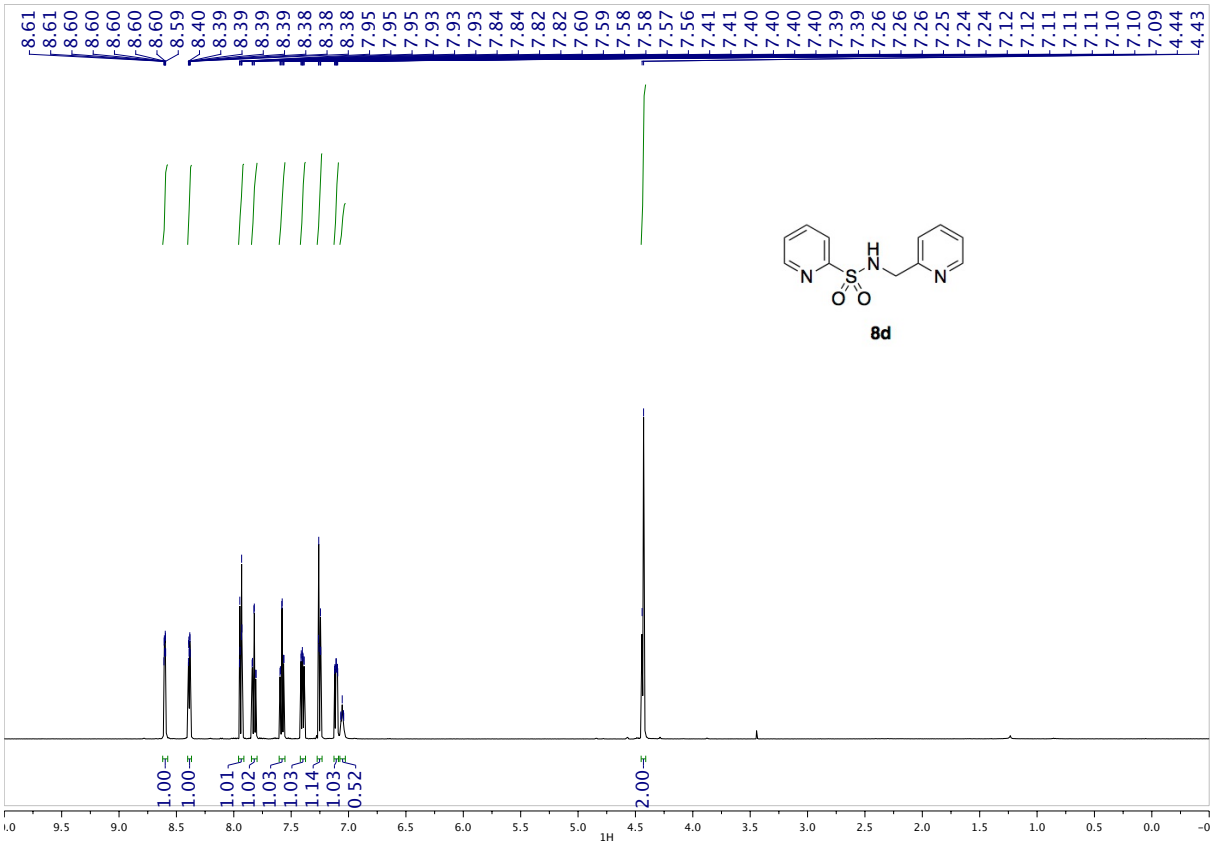
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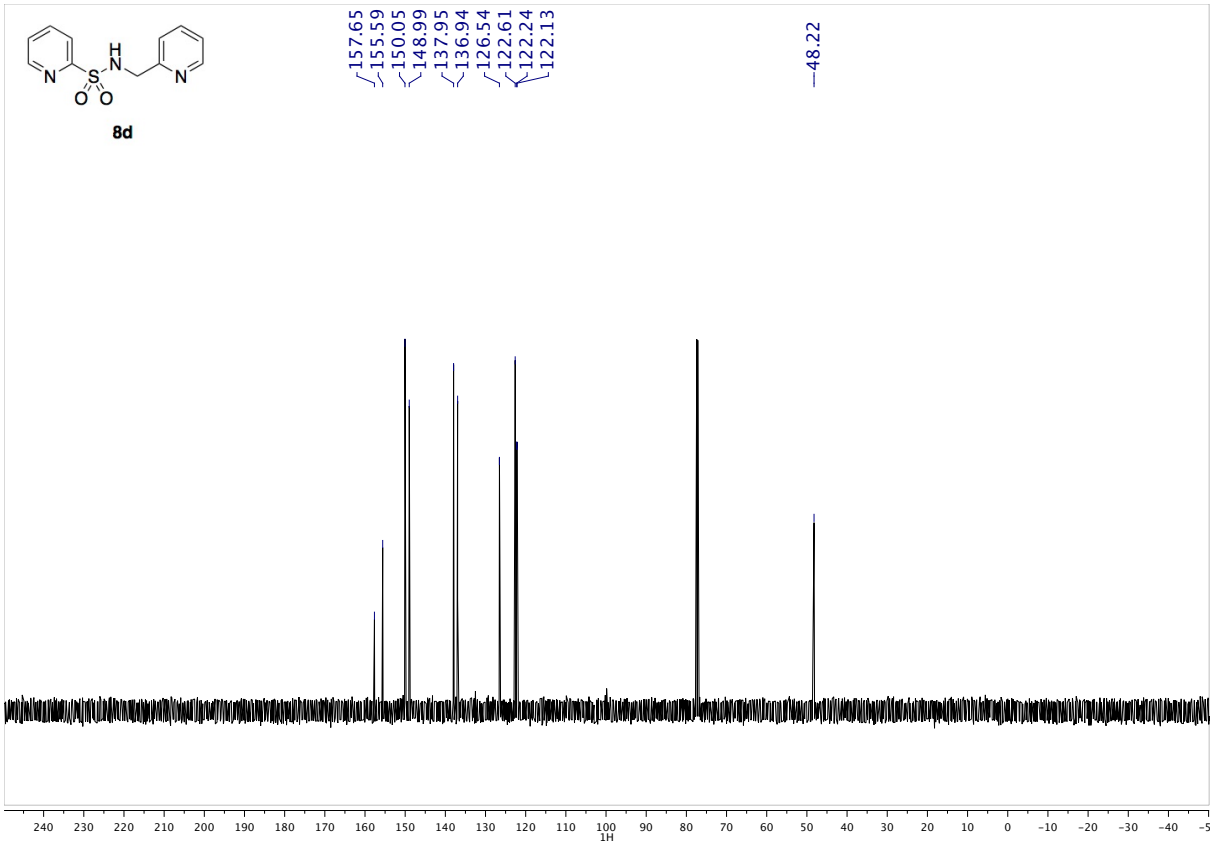
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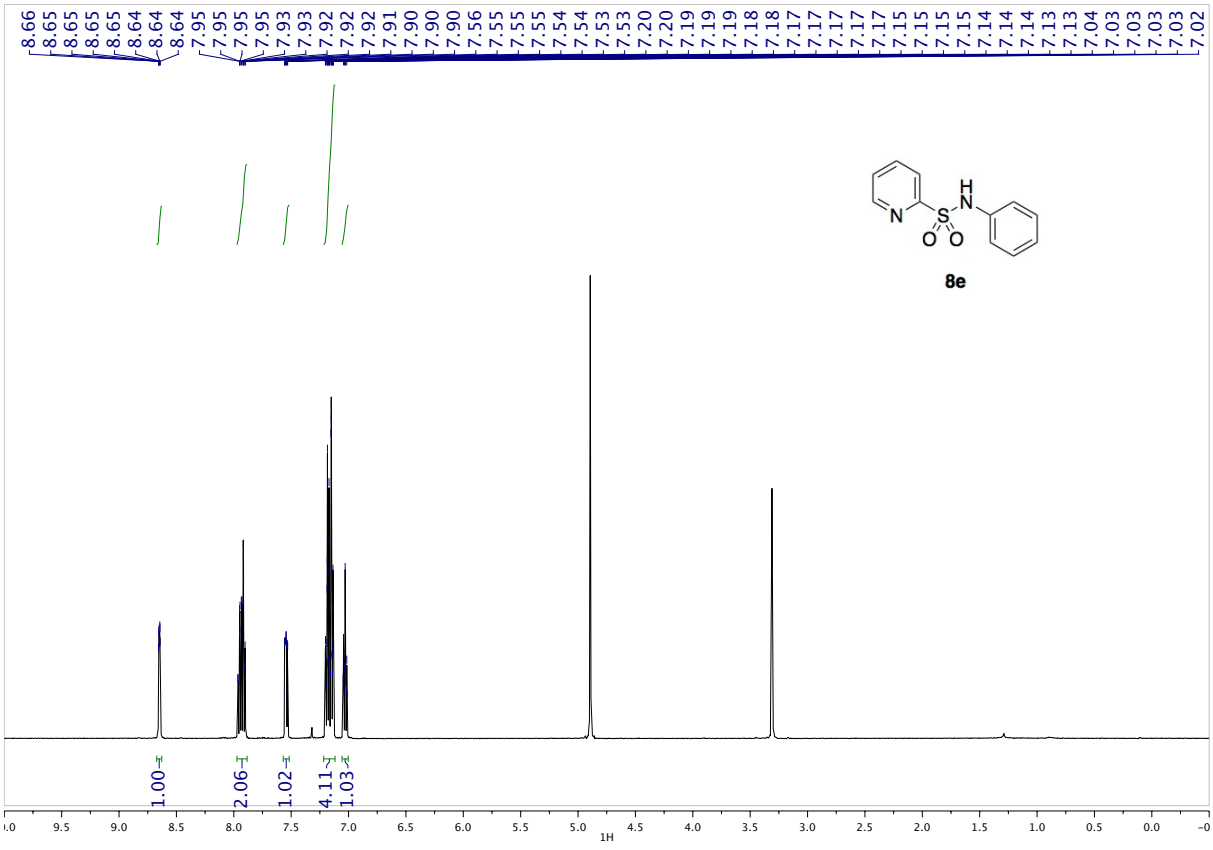
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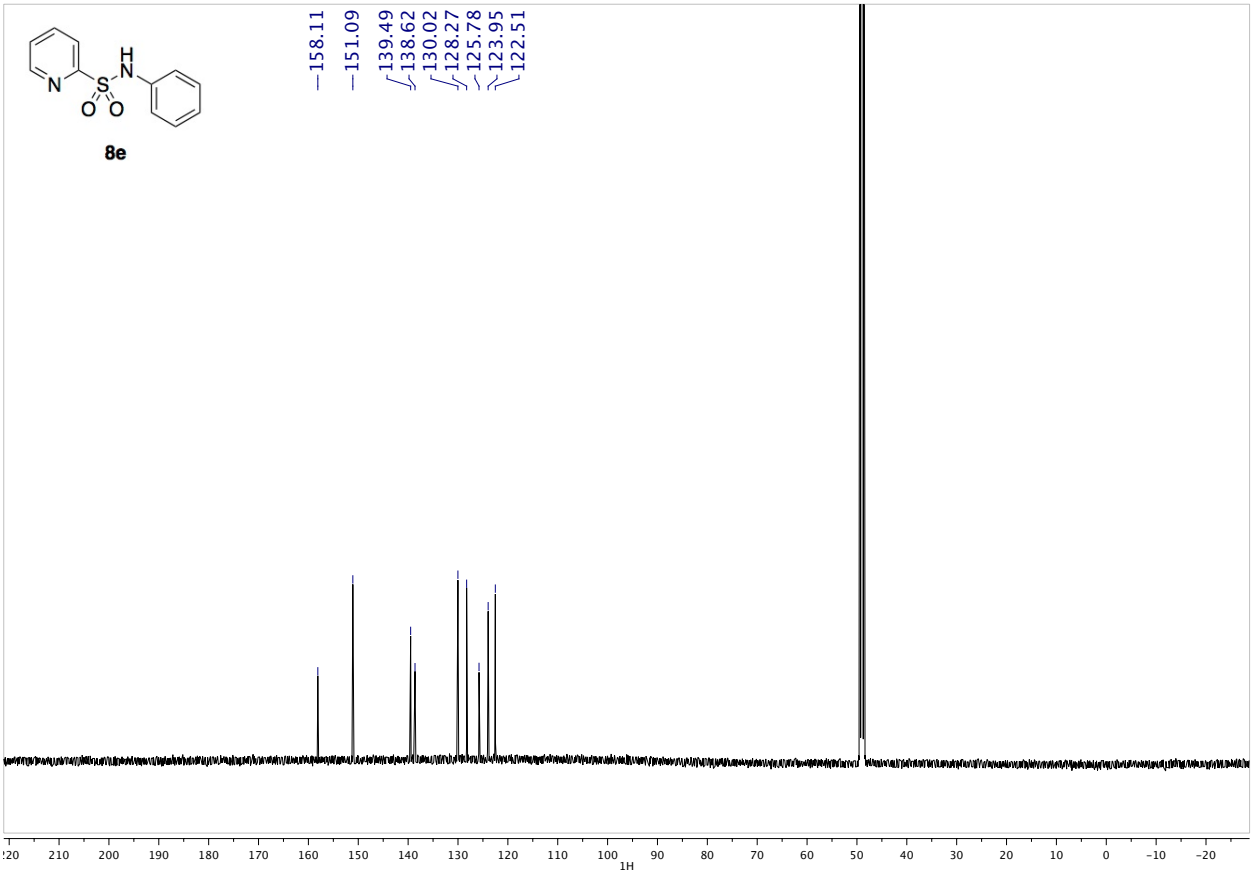
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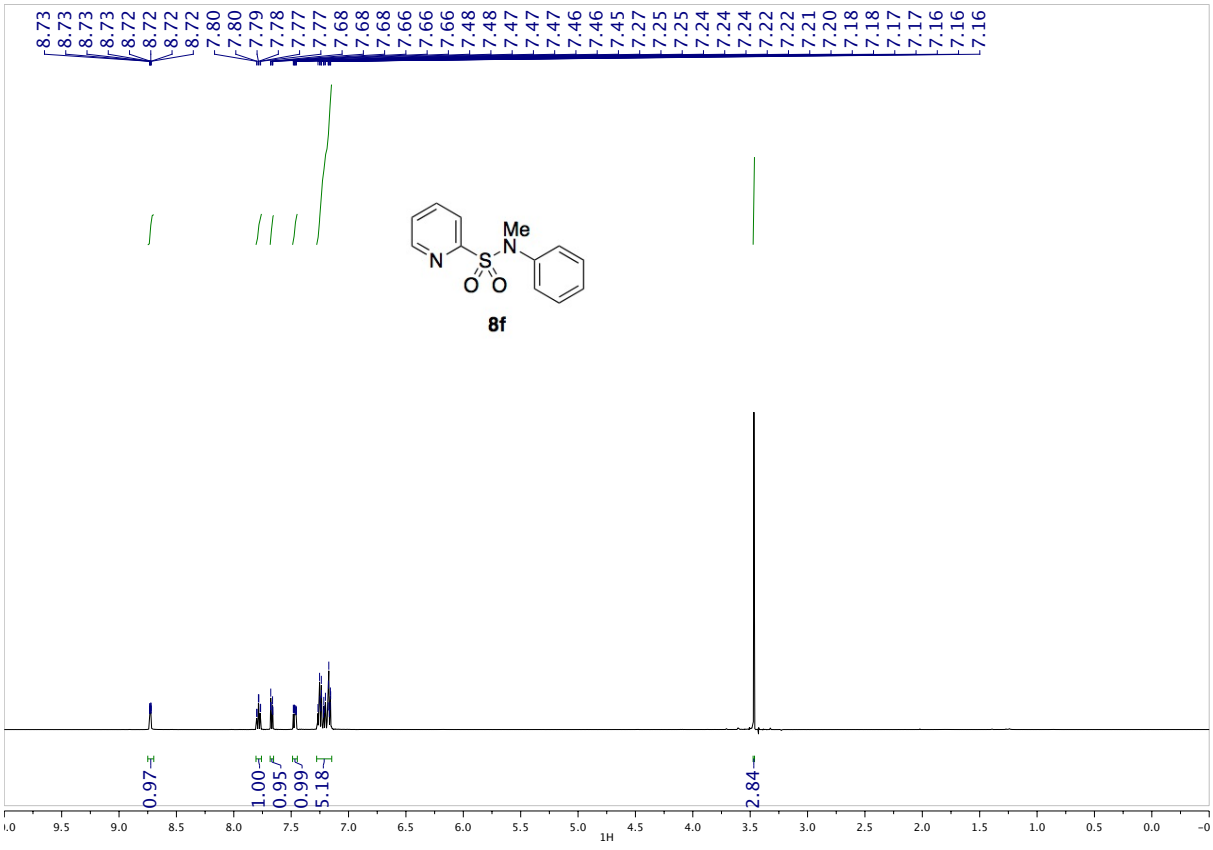
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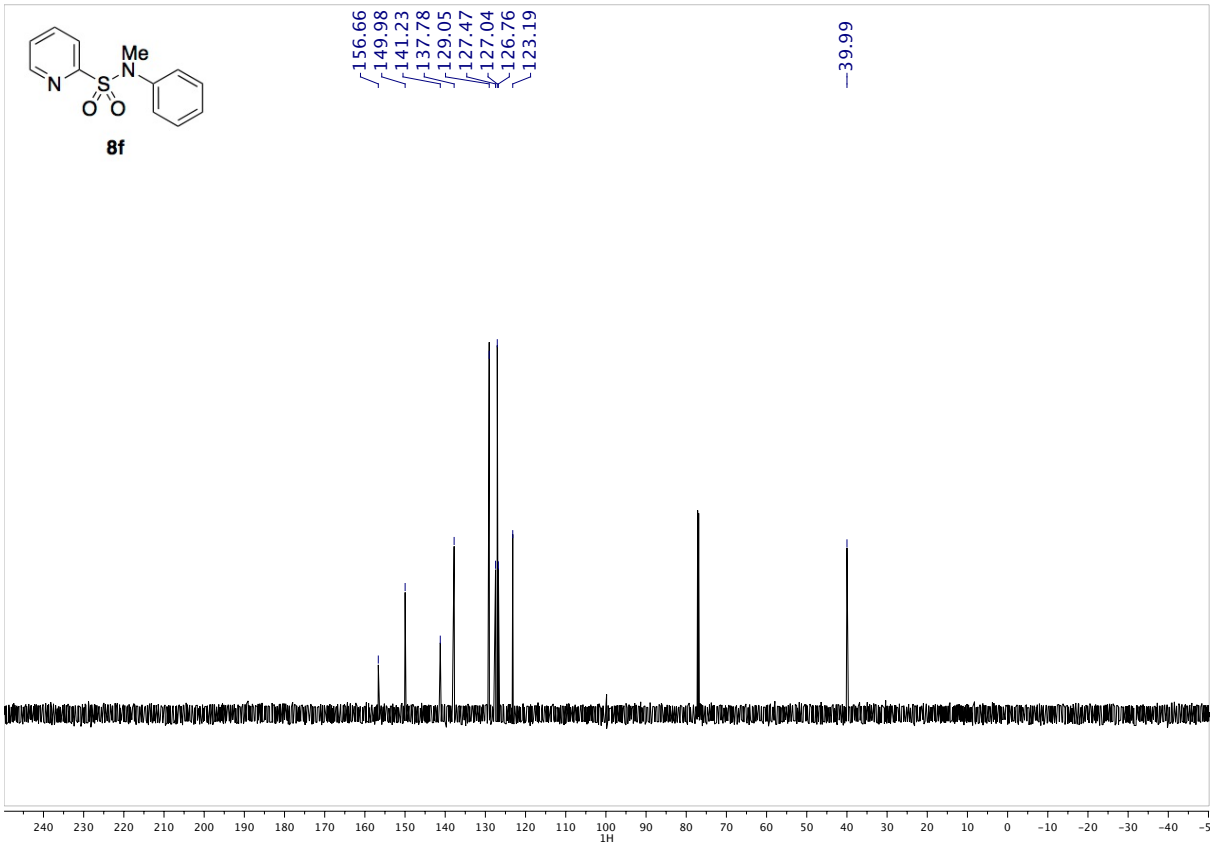
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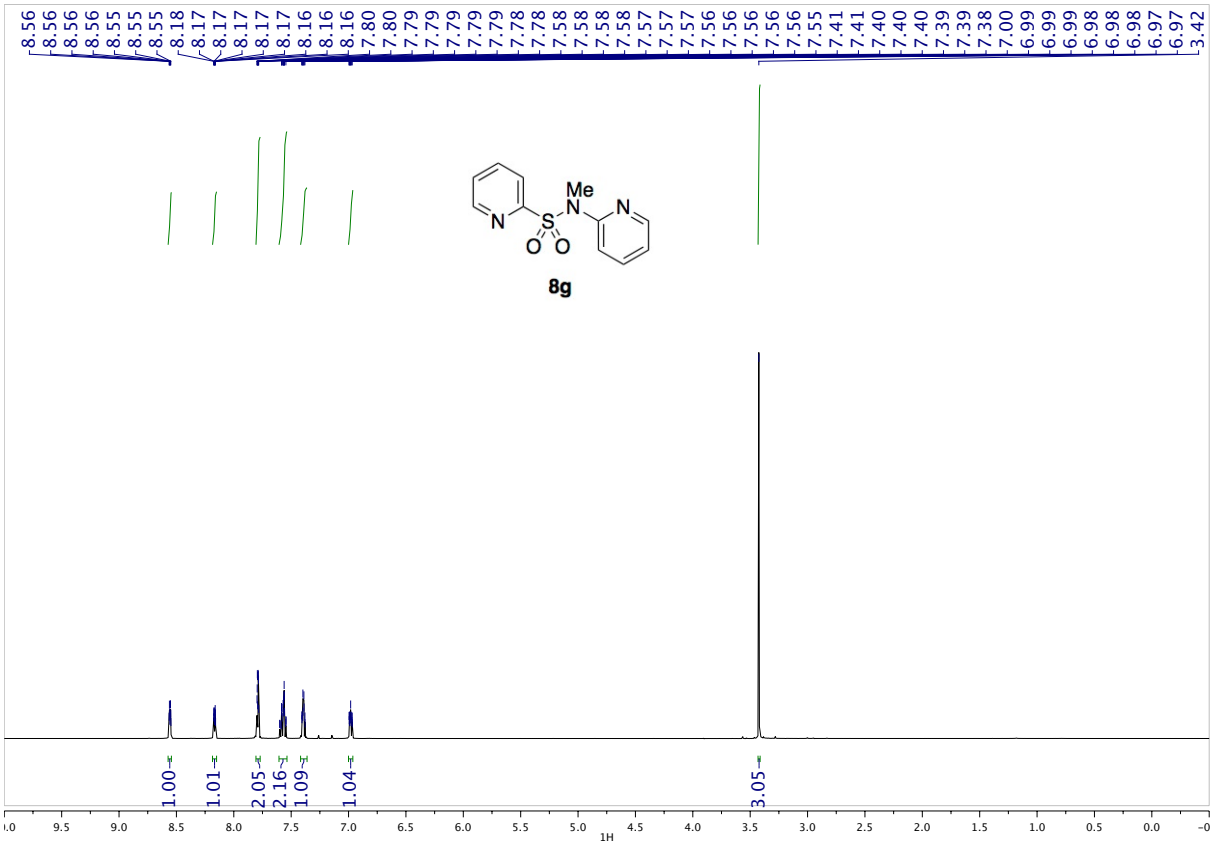
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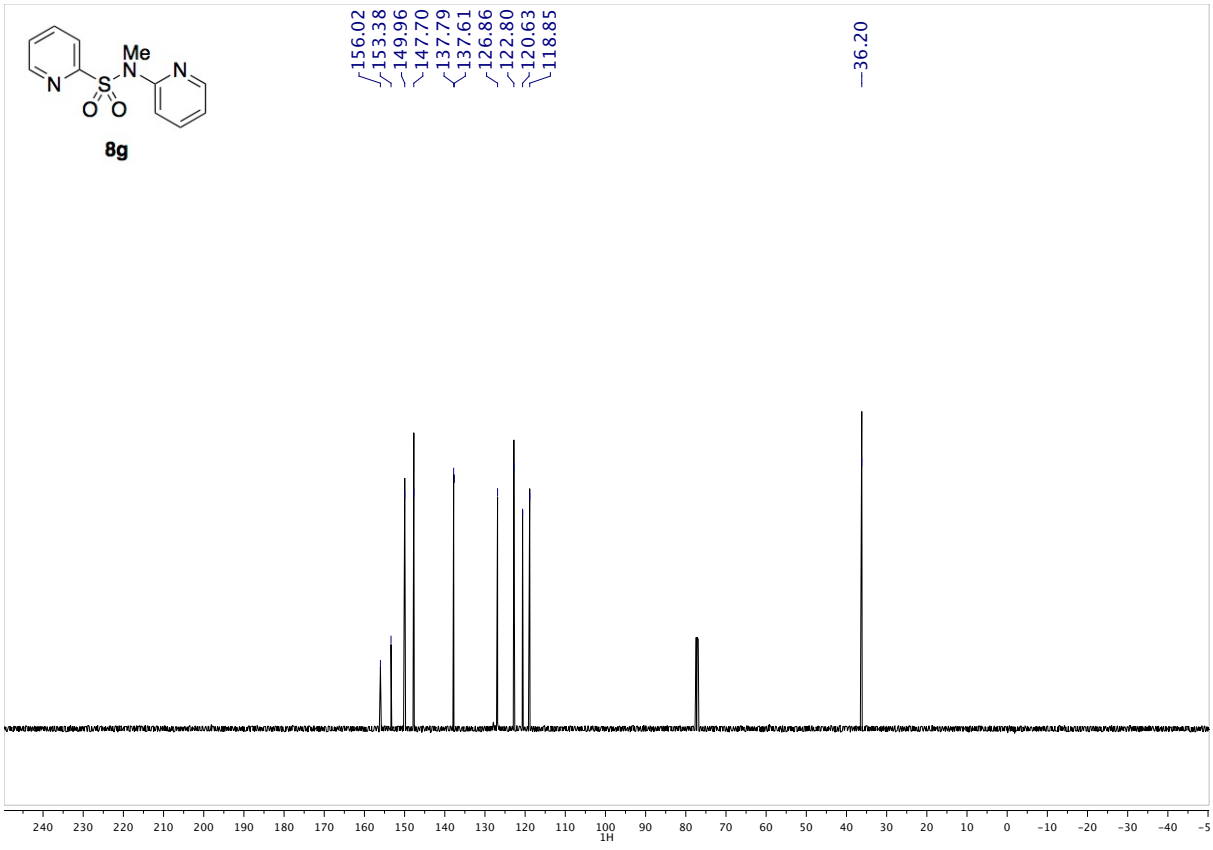
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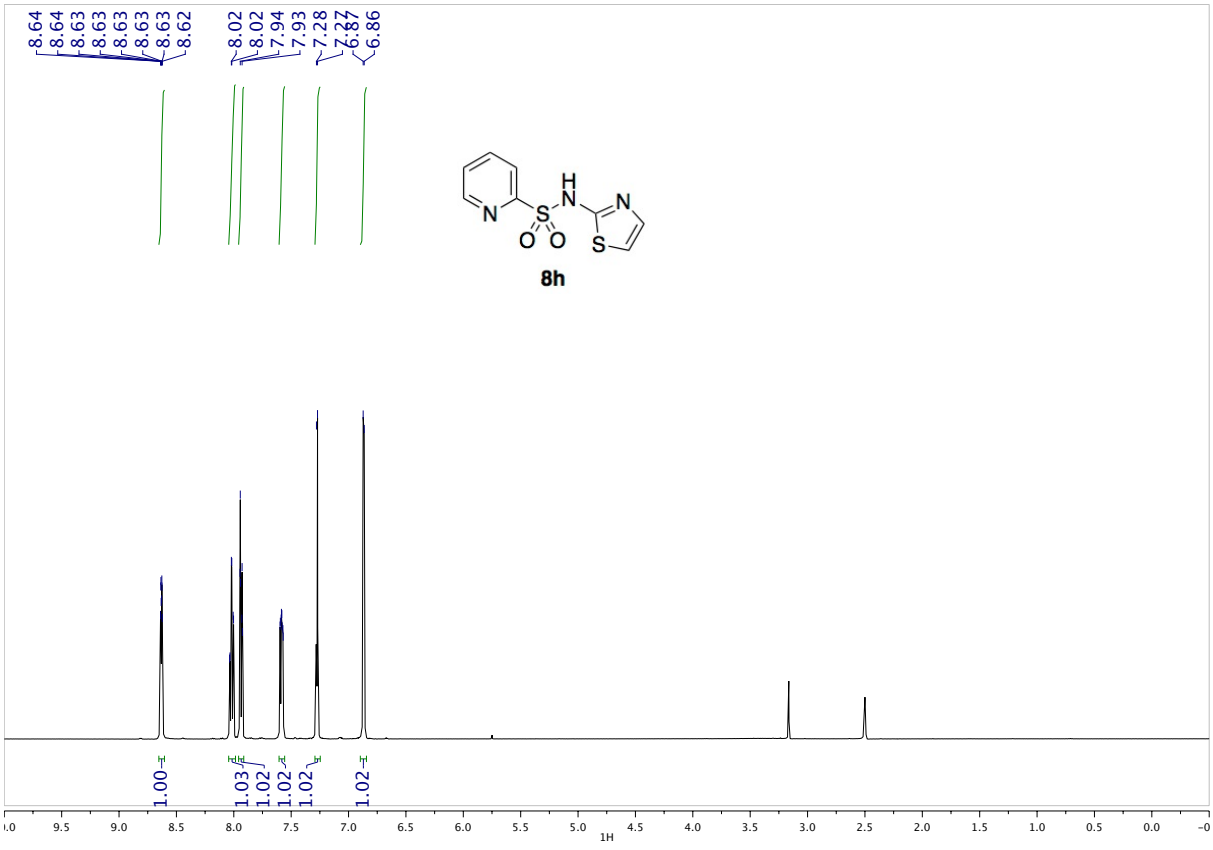
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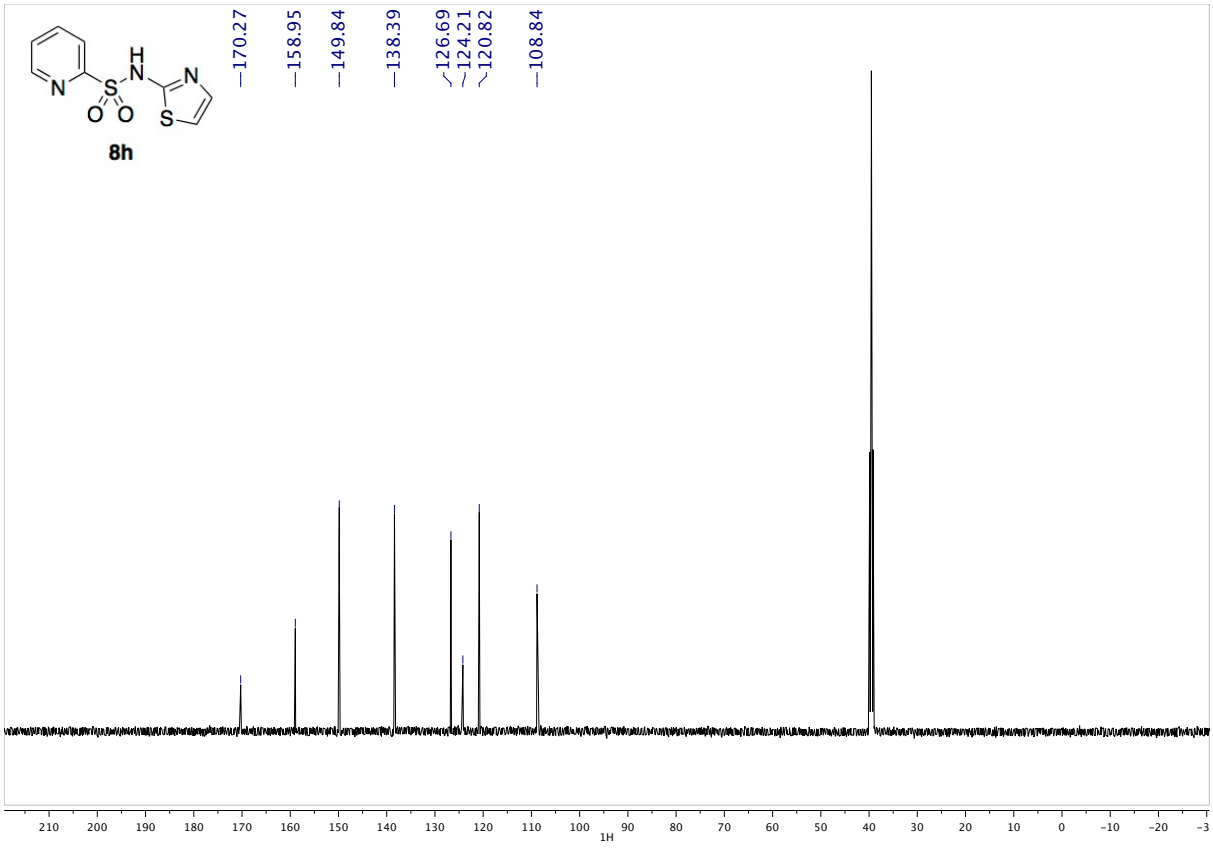
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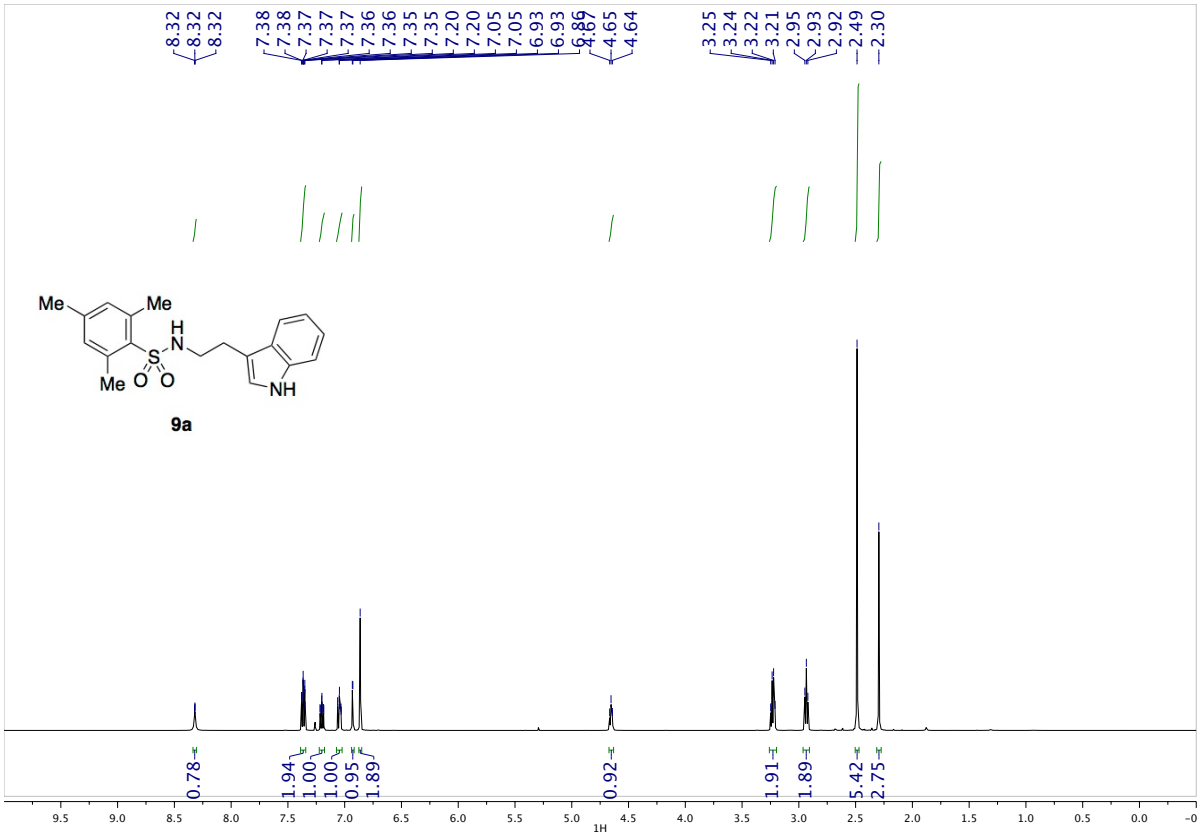
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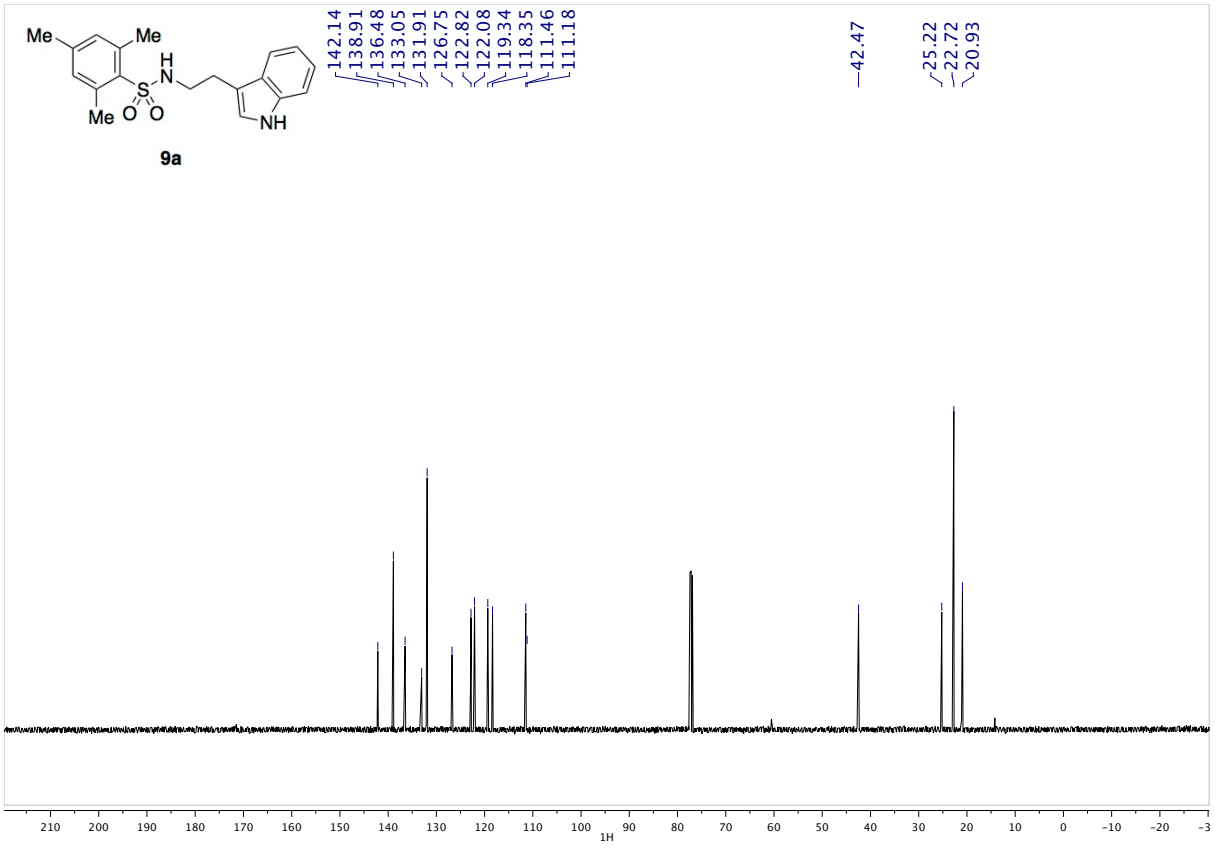
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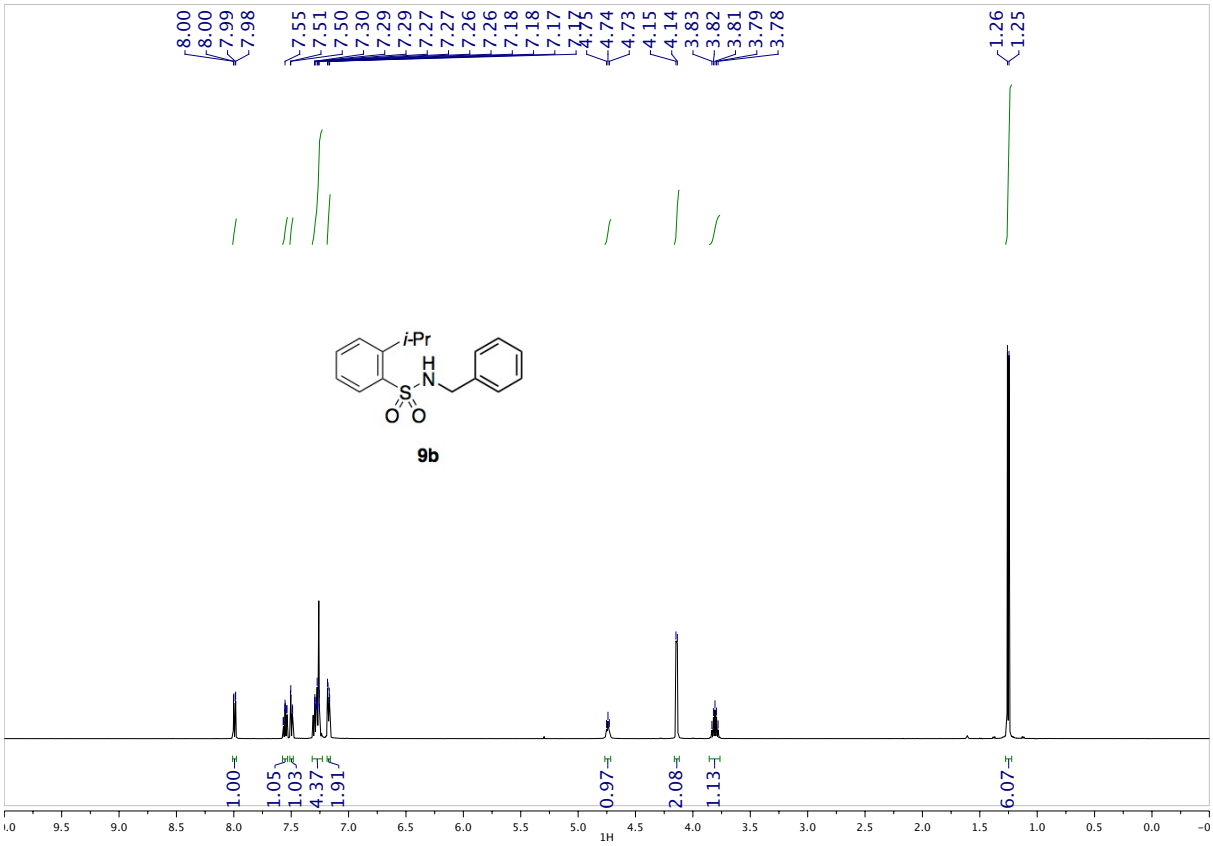
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H
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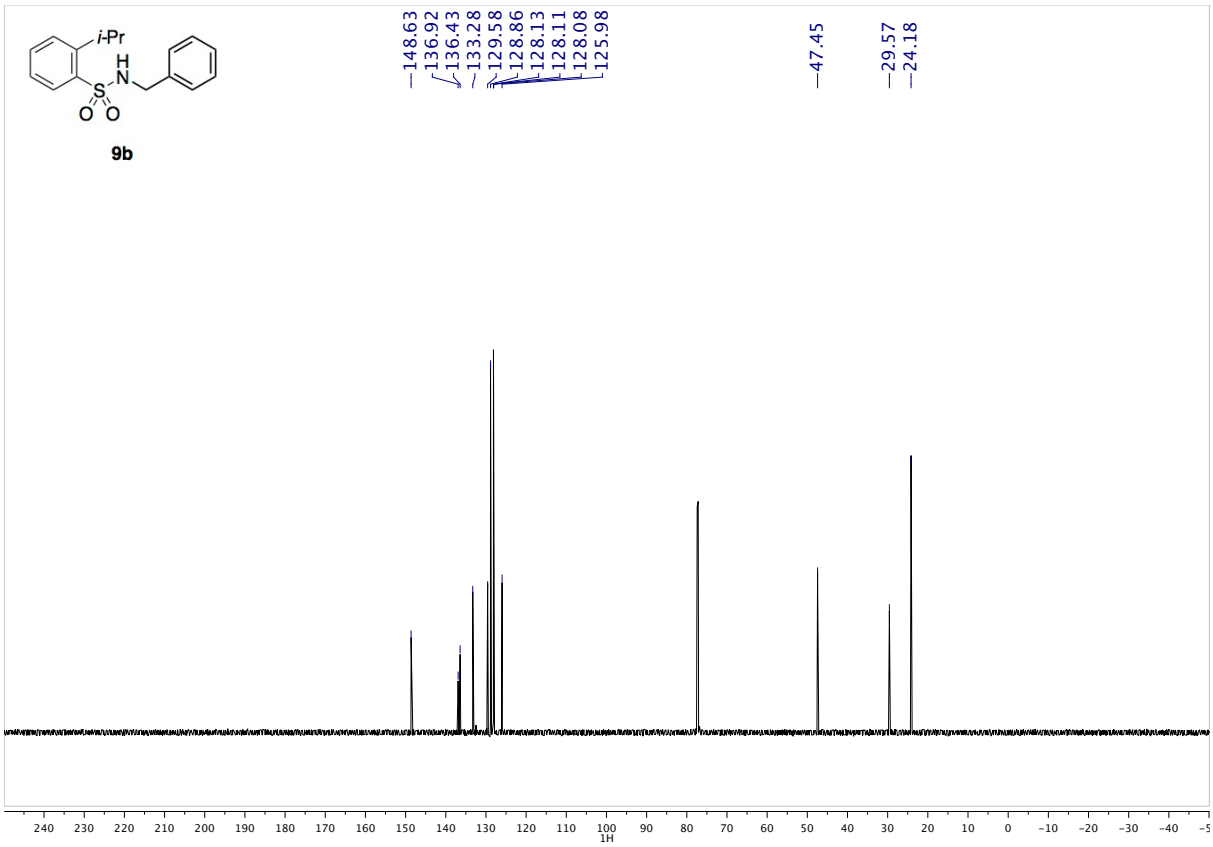
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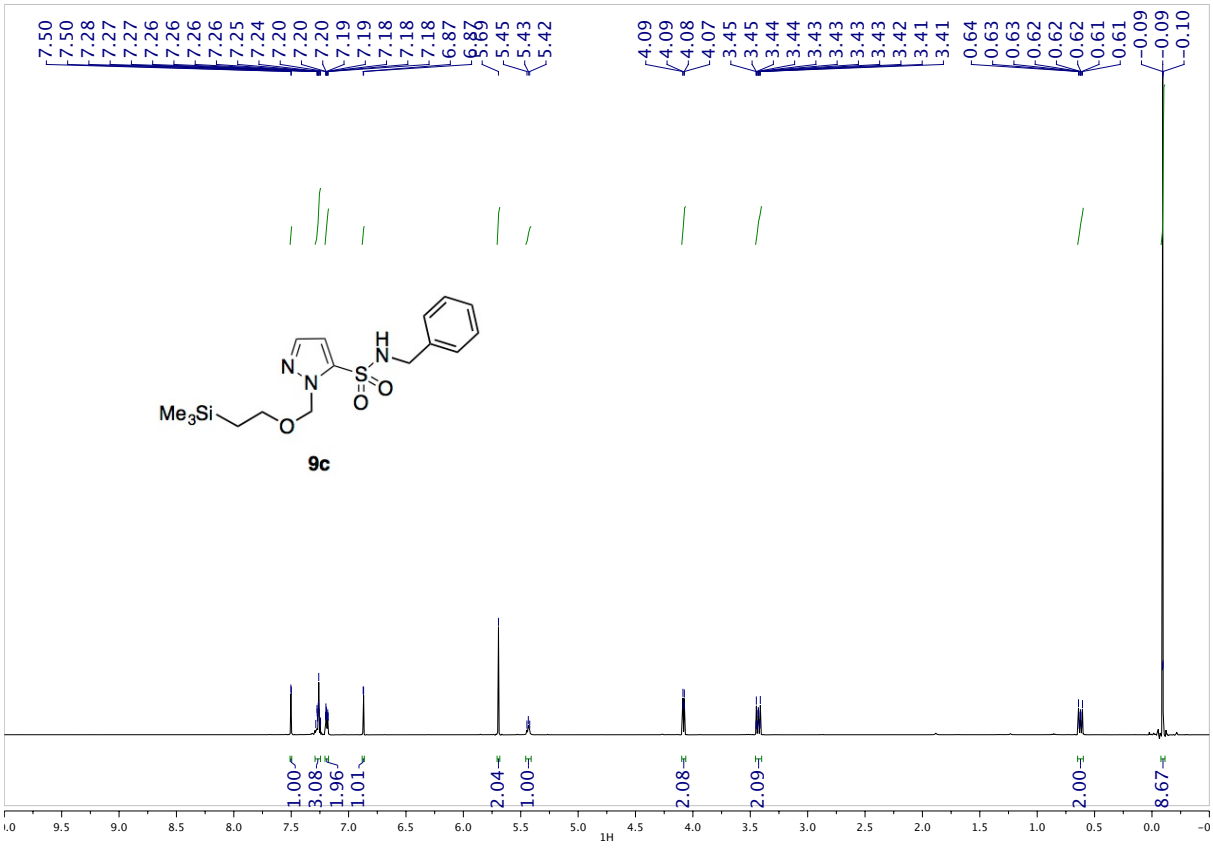
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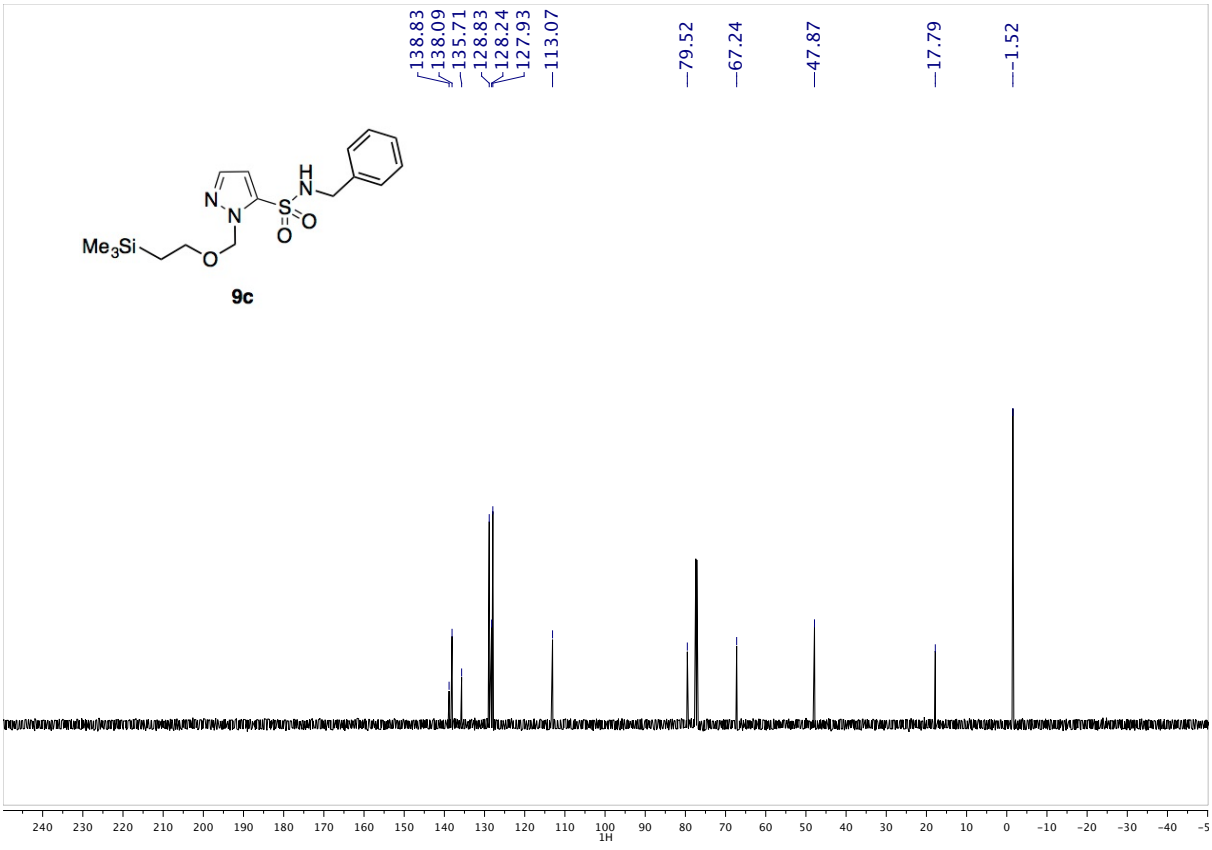
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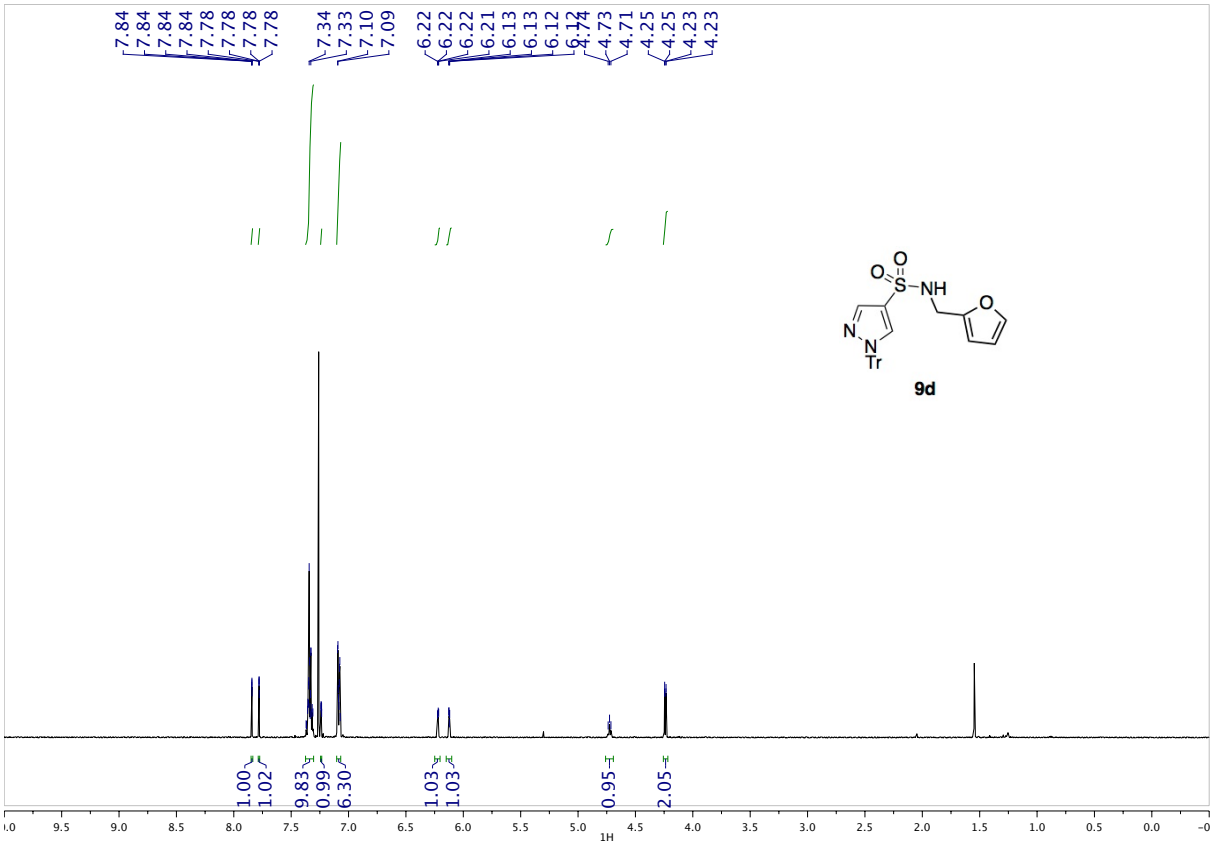
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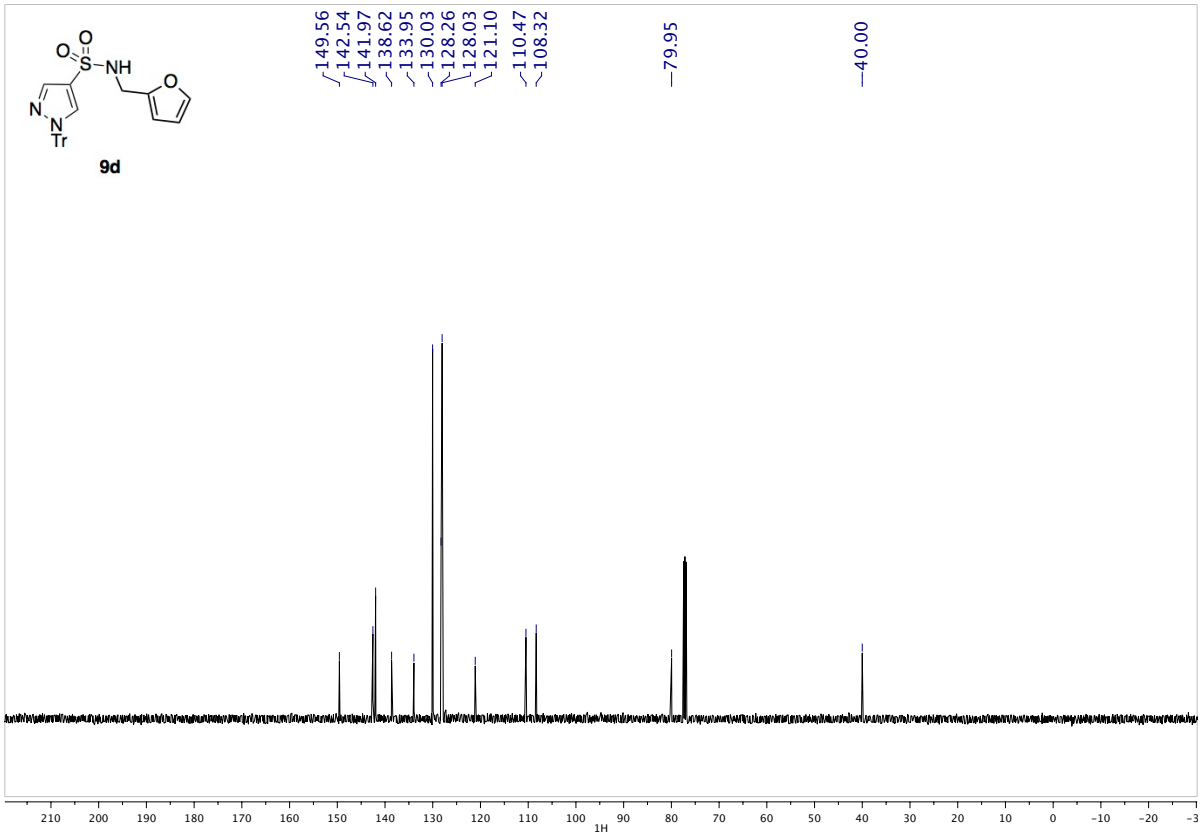
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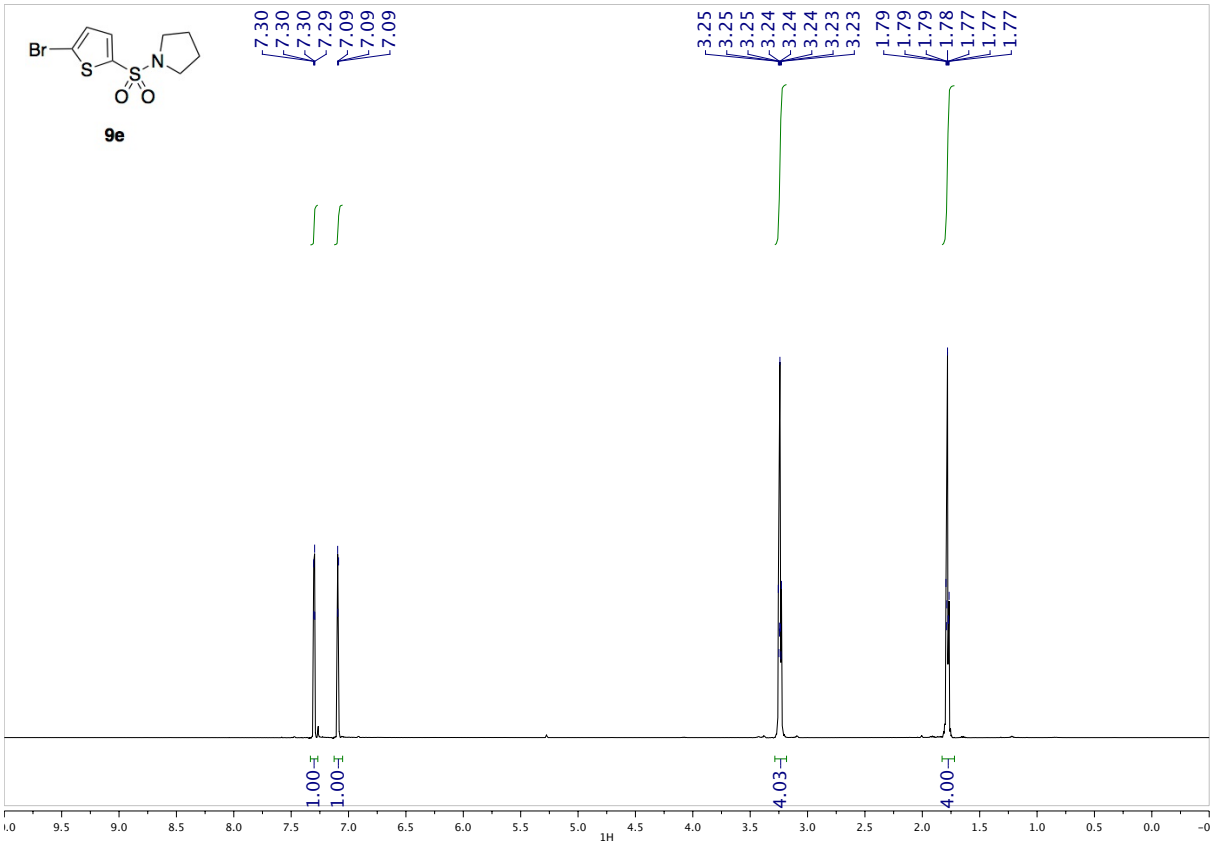
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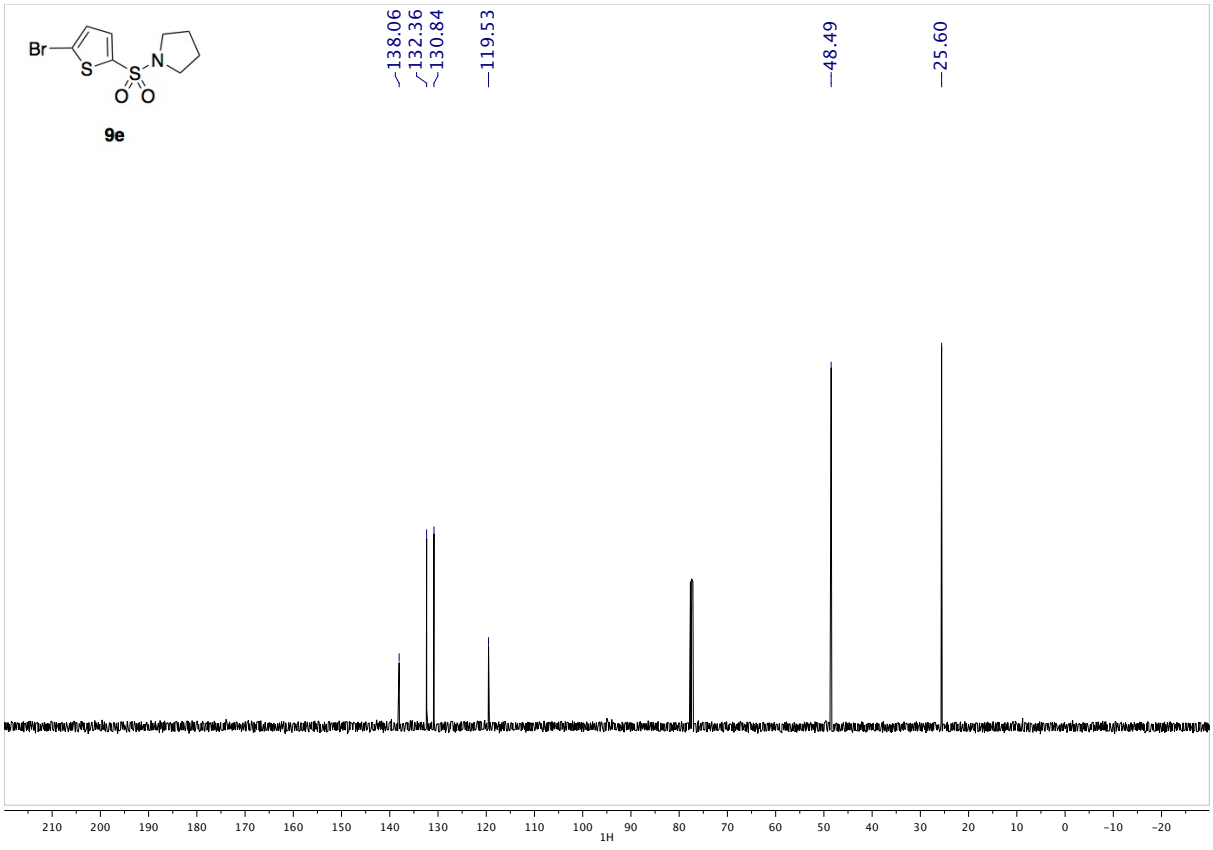
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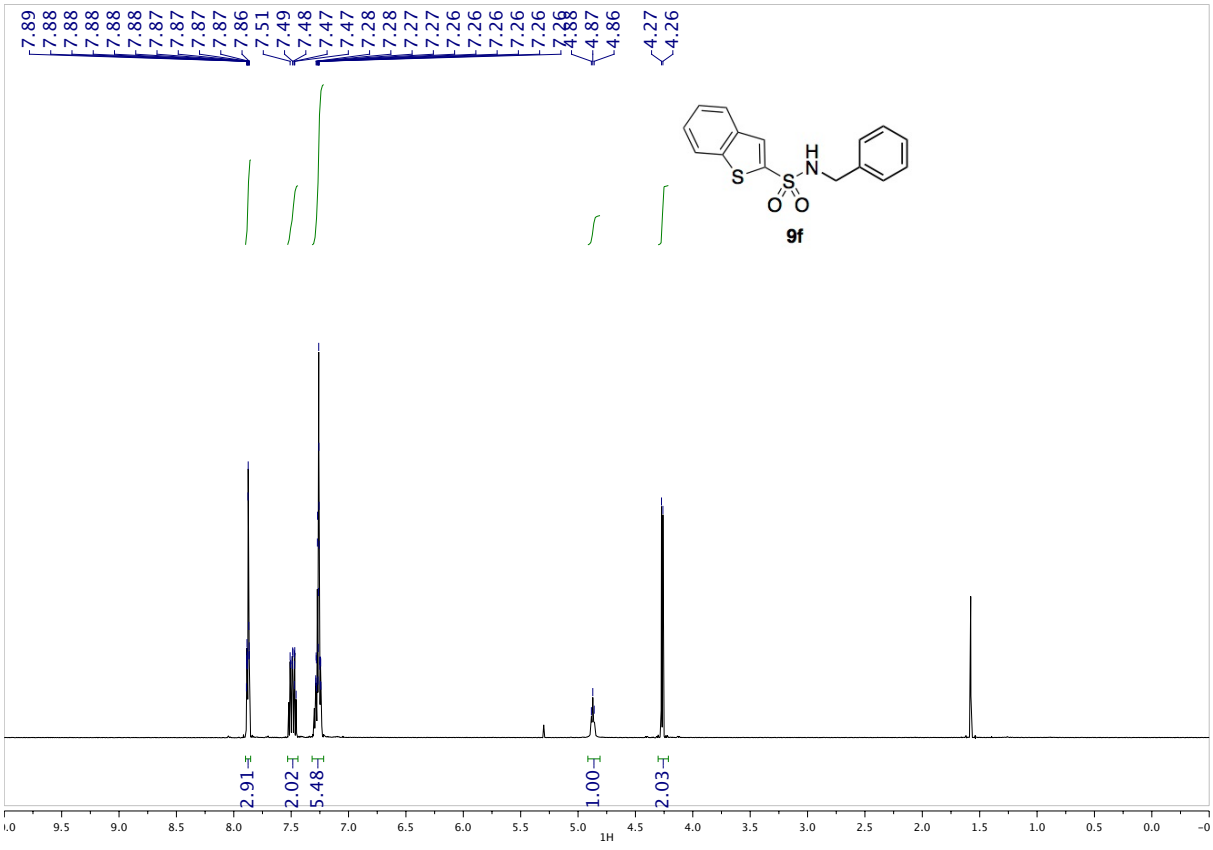
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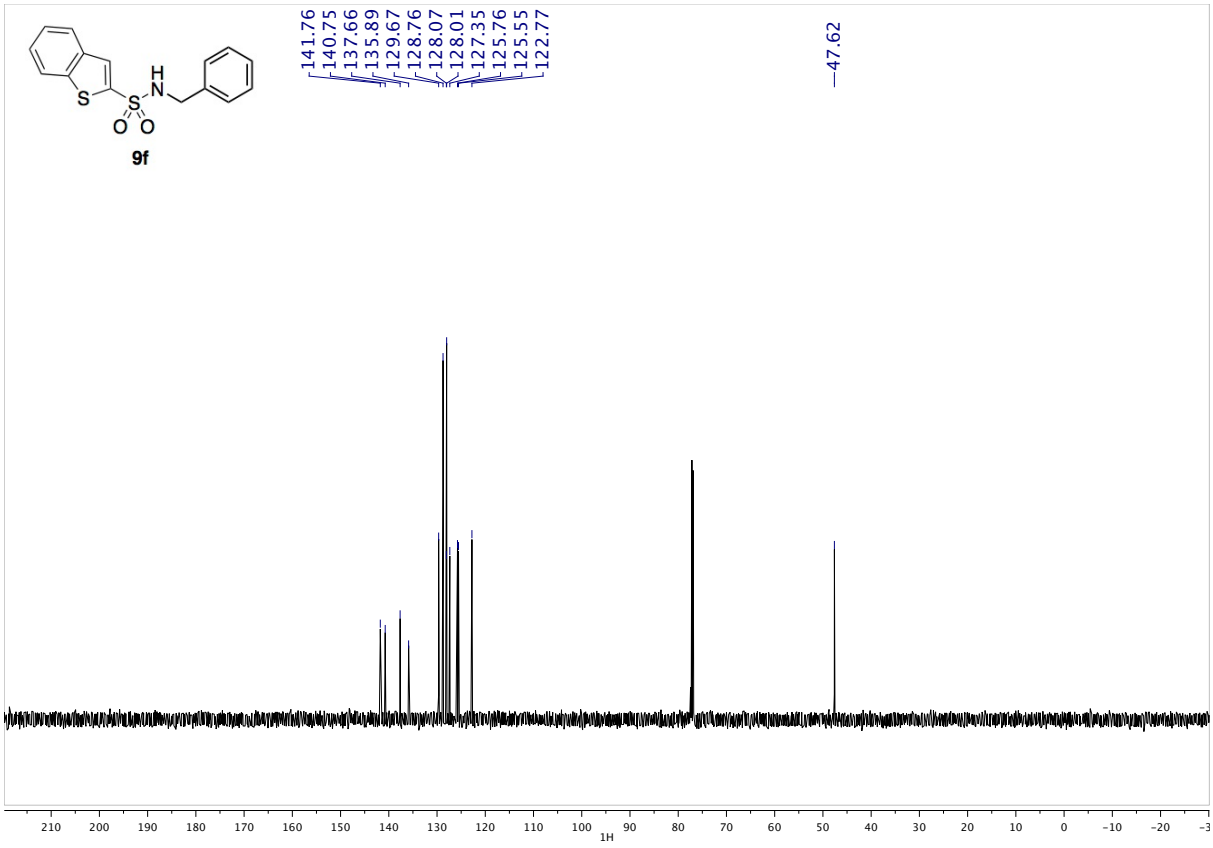
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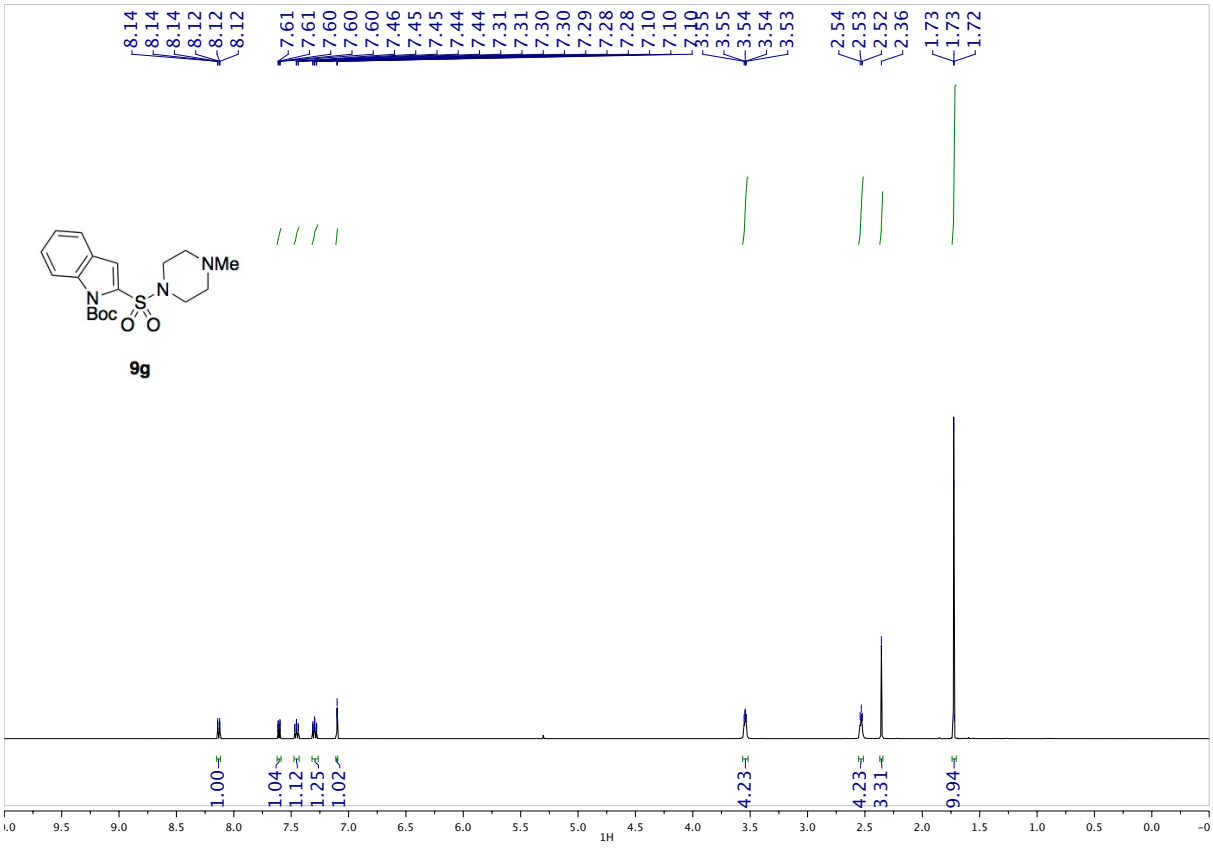
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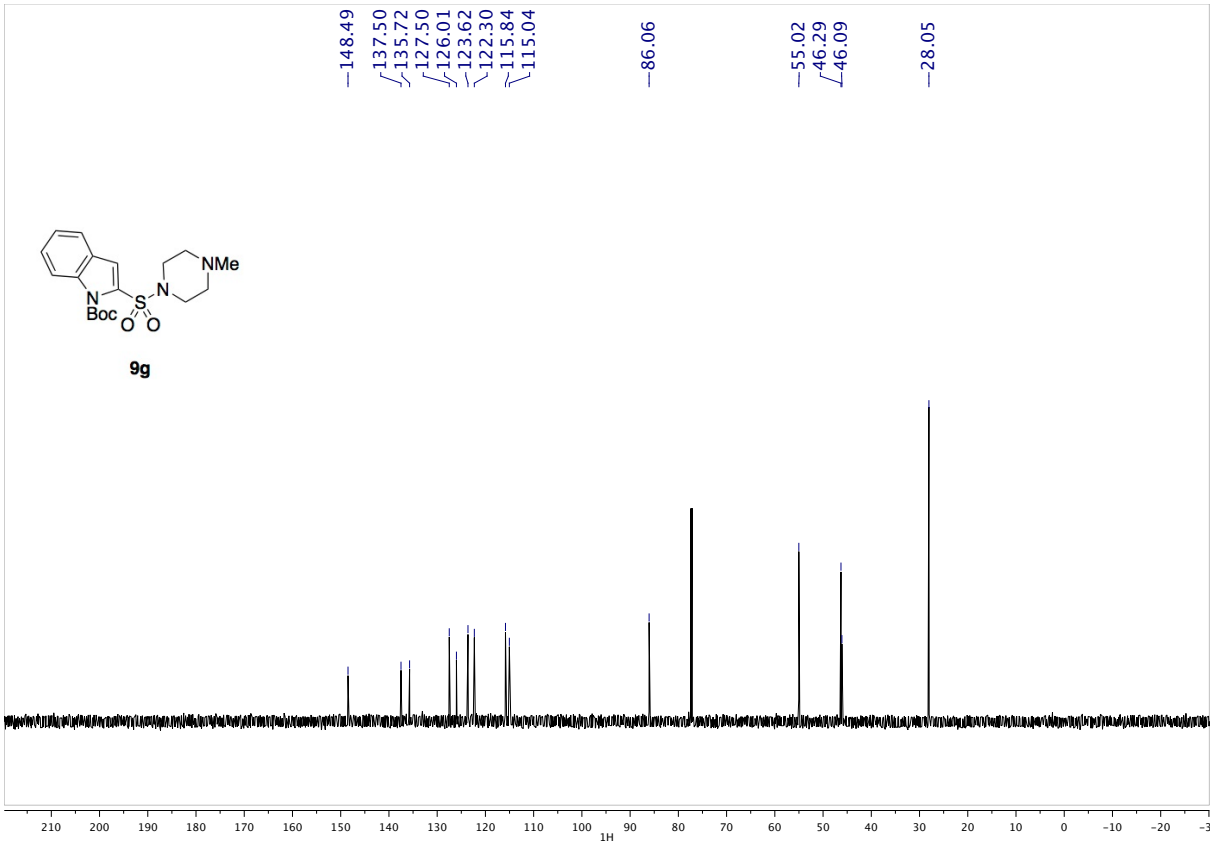
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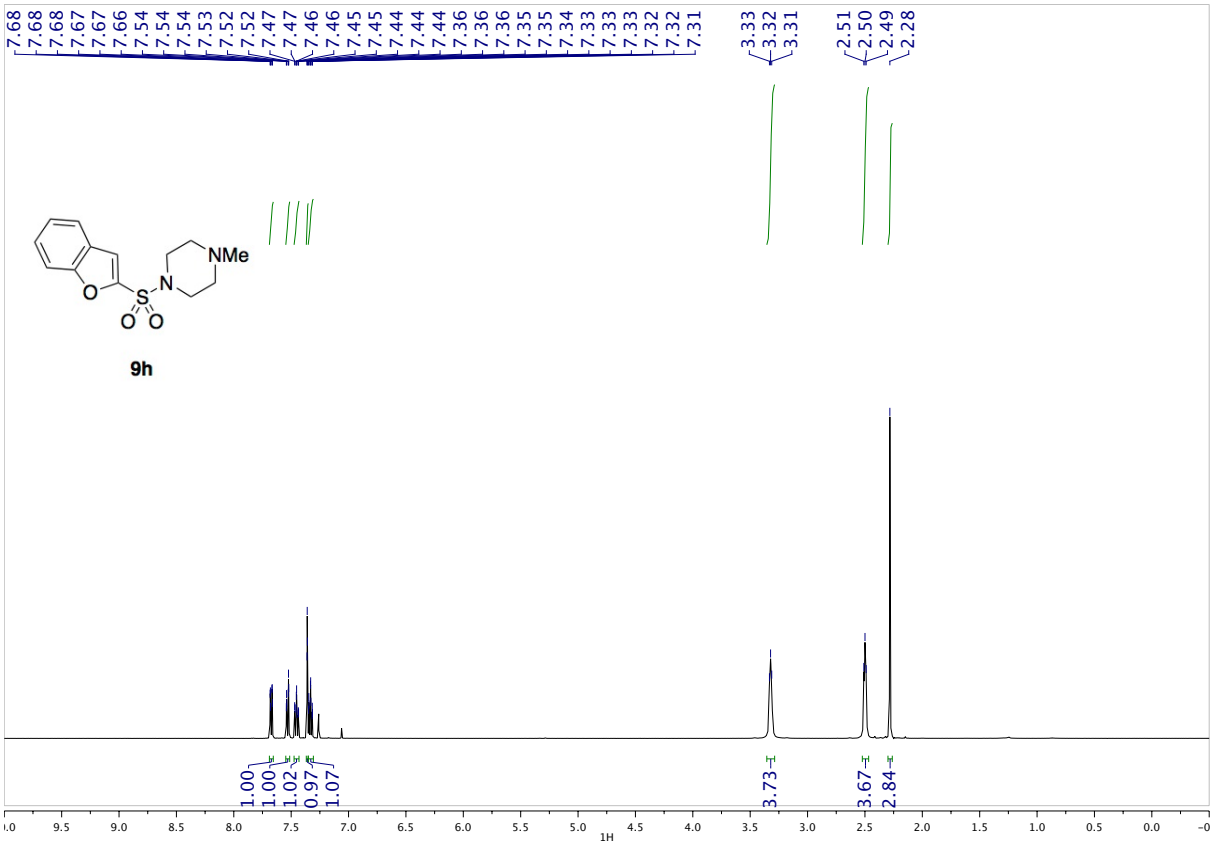
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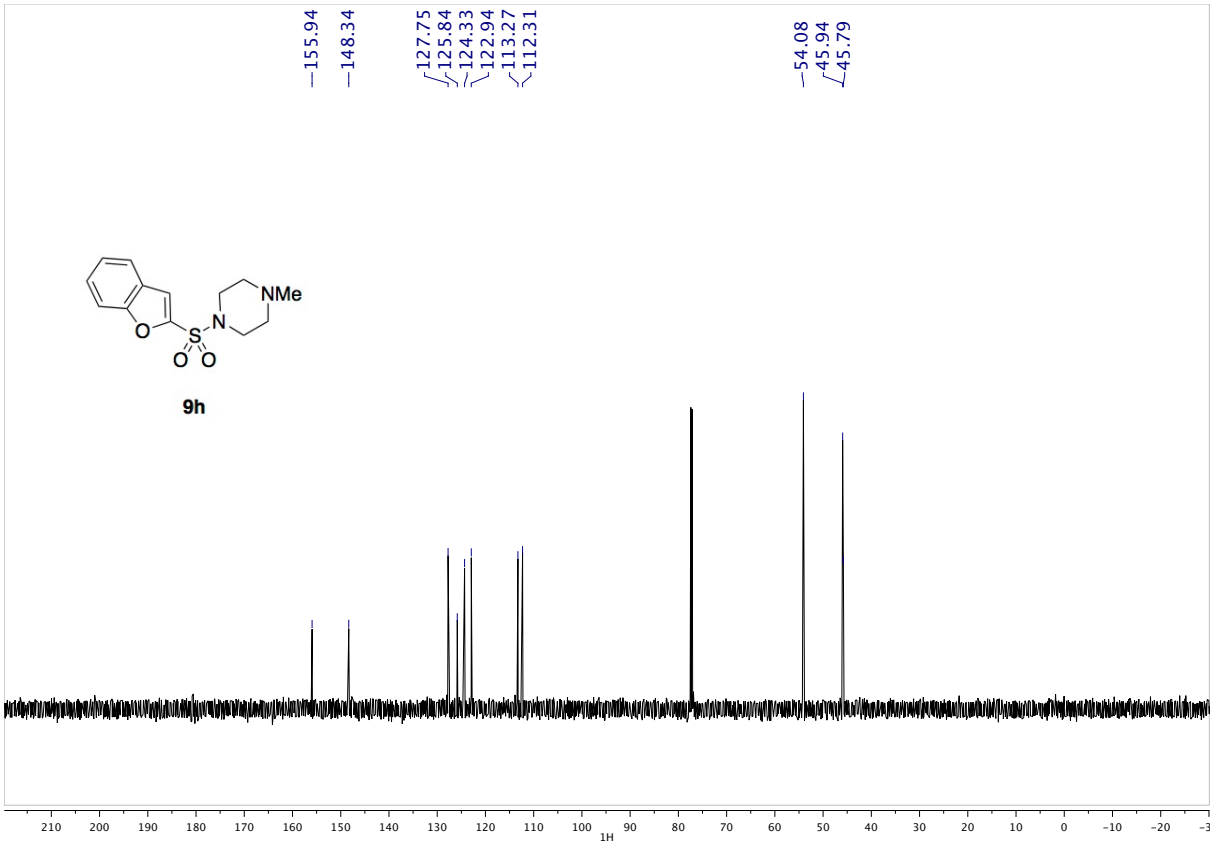
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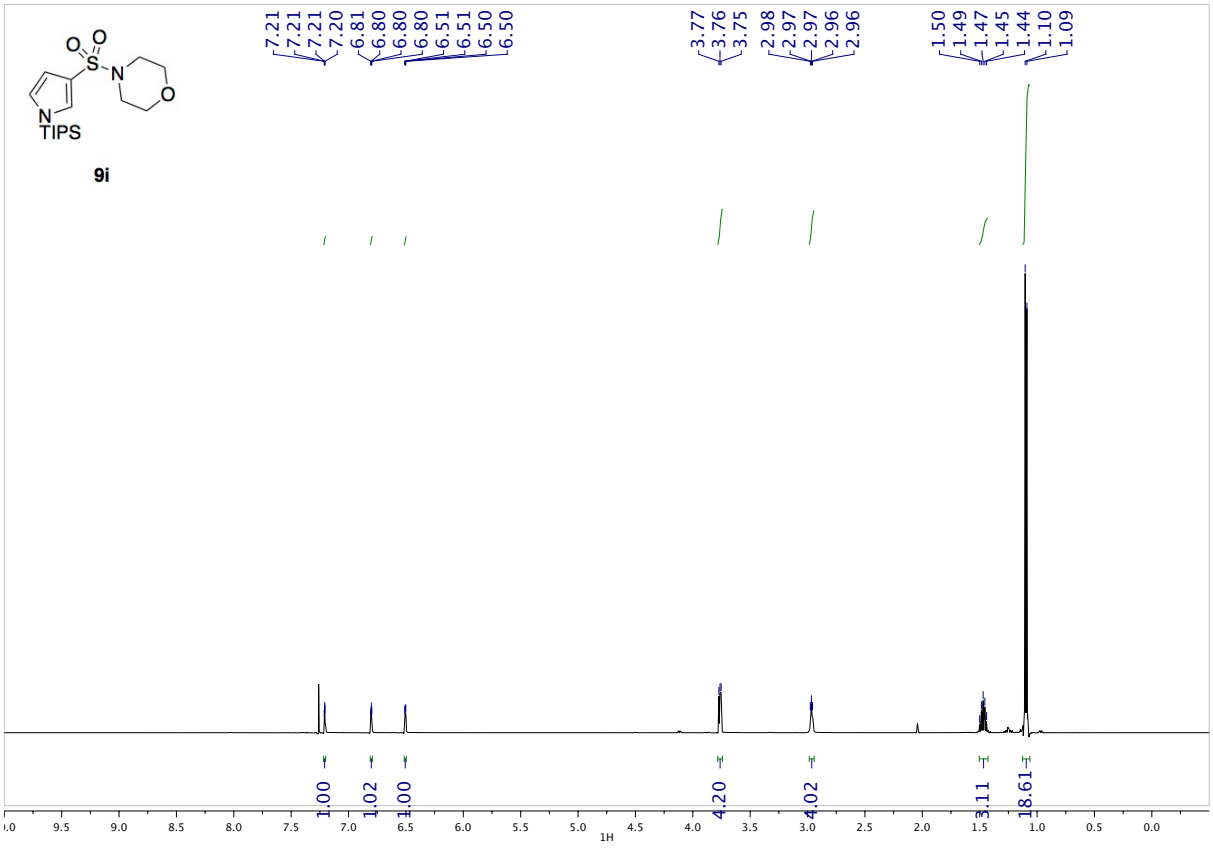
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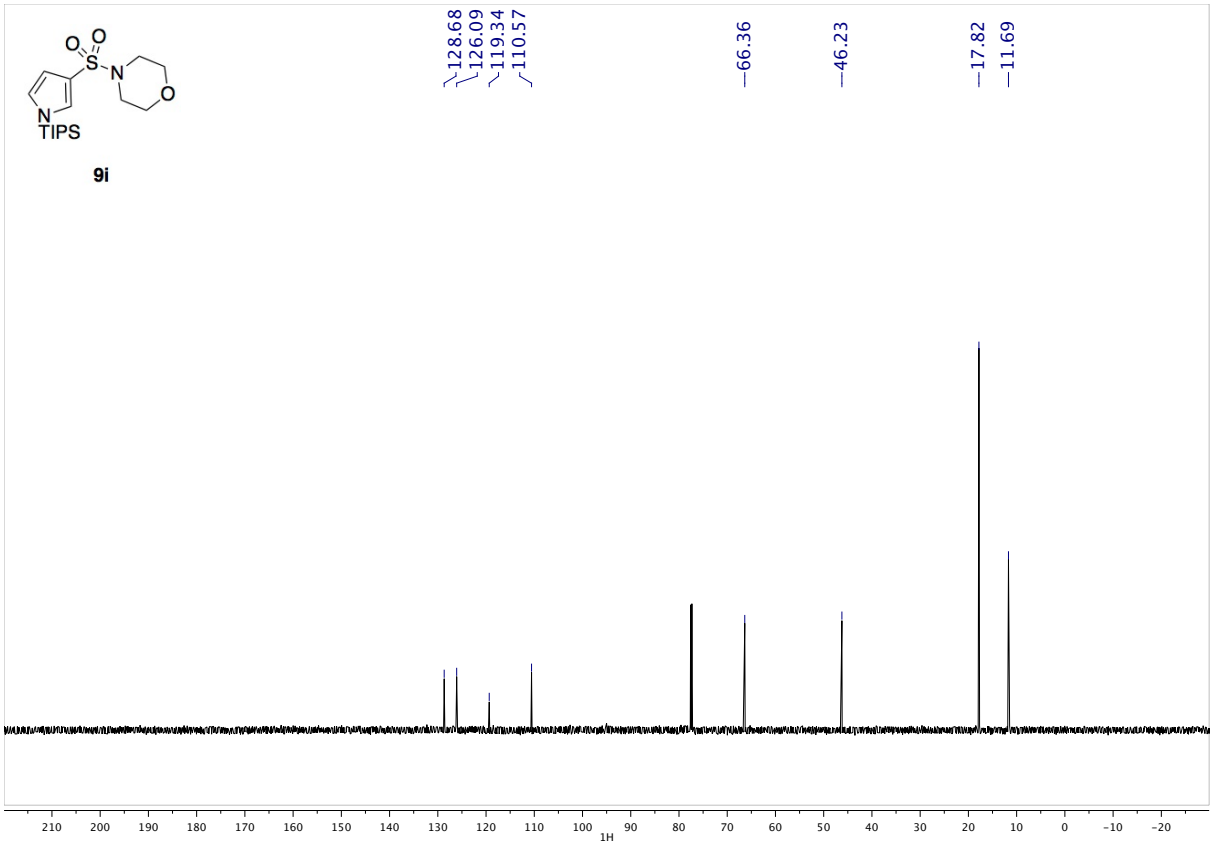
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